FY 2002 ORWH-SUPPORTED RESEARCH INITIATIVES

AGING

TITLE: Aging of Brain: Effects of Prenatal Nutrition — **NIA**
P.I.: Jan Blusztajn, Ph.D.
INSTITUTION: Boston University, MA
GRANT NO.: 2PO1AG09525 -11
KEYWORDS: Prenatal nutrition, choline, folic acid, nutrition, neurosciences research, aging
TYPE STUDY: Basic
AMOUNT: $100,000

The goal of this study is to determine the mechanisms by which the availability of choline and folic acid during the prenatal period modifies brain structure and function in development, adulthood and old age. The proposed studies will 1) determine the molecular mechanisms involved in the brain reorganization that is governed by choline and folate availability by studying signal transduction pathways and developmental patterns of gene expression in brain; 2) measure synaptic function and plasticity in hippocampus of rats exposed to varying levels of choline or folate in utero; 3) examine age-related changes in conditioned stimulus processing (attention) as a function of the prenatal availability of choline and folate; 4) determine if supplementation with folate in early development leads to lifelong changes in spatial memory, brain anatomy and neurochemistry; 5) investigate whether choline supplementation either prenatally or across the lifespan ameliorates behavioral, anatomical, and biochemical deficits seen in mice lacking the apolipoprotiein E.

TITLE: A Fall Prevention Program for High Risk Elderly Women — **NINR**
P.I.: Jean F. Wyman, Ph.D., R.N.
INSTITUTION: University of Minnesota, Minneapolis, MN
GRANT NO.: 5R01NR005107-03
KEYWORDS: injury prevention, nursing intervention, clinical research, aging
TYPE STUDY: Clinical
AMOUNT: $150,000

The long term objective of this study is to develop cost-effective, community-based strategies for the prevention of falls in high risk elderly women. Specific aims: 1) Test the efficacy of a fall prevention program for high risk elderly women on fall rates over one and two years; 2) Determine the effects of the fall prevention program on postural competence, functional performance, and a variety of other outcome measures; and 3) Identify demographic, clinical, personal, functional, and postural competence variables that predict long-term exercise adherence for participants in the fall prevention program. The participants will be 250 community-dwelling women who are aged 70 and over, mentally intact, ambulatory, with postural instability and at least one other fall risk factor, not currently involved in regular exercise, and medically stable with physician approval for independent exercise participation. This study will provide information on the efficacy and cost of simple interventions designed to prevent falls and fall-related injuries, reduce preclinical disability, maintain long-term exercise adherence, and improve quality of life for older women.

ALCOHOL AND OTHER SUBSTANCE ABUSE

TITLE: Biobehavioral Trajectories to Alcohol Abuse: A Pilot Study — **NIAAA**
P.I.: Roberta Palmour, Ph.D.
INSTITUTION: McGill University, Montreal, Quebec Canada
GRANT NO.: 1R21AA013647-01
KEYWORDS: alcohol addiction, risk factors, environmental factors, gender
TYPE STUDY: Basic
AMOUNT: $100,000

Adolescent alcohol abuse has now reached epidemic proportions, carrying with it a toll of lost opportunity, suffering and death. Many studies document the correlation between early alcohol use and later alcohol dependence, and a widespread belief that delaying the onset of alcohol consumption until the end of adolescence will reduce the risk of pathological drinking. An alternate interpretation is that those who drink early are those who are especially vulnerable, either through biology or circumstance. There are major implications of these conflicting explanations for treatment, for research and for public policy. To disaggregate the influence of specific biobehavioral and sociocultural variables in any appropriate cross section of the human population is exceedingly difficult. A pilot study of the feasibility of addressing this question experimentally by capitalizing upon an animal model of spontaneous alcohol abuse is proposed. C. aethiops, a non-endangered African primate, is highly homologous with man, lives in social groups, has a distinct adolescent period in its ontogeny, and contains individuals who differ from one another with respect to alcohol consumption and to behavioral traits (sociability, excitability, etc.) In an 18-month cross-sectional study 96 male and female vervet monkeys will be housed in groups balanced by sex, level of baseline alcohol consumption and temperamental behavioral profile. The manipulated factor will be exposure to ethanol and to drinking or non-drinking role models. The principal outcome measure (9 and 18 months later) will be quantity and pattern of ethanol consumption; weekly social behavioral measures will also be collected in standard primatological fashion. Evaluation of the independent or joint effects of gender, behavioral trait status, and

initial propensity to drink and of exposure to ethanol or drinking role models will utilize multivariate regression methods. In a second phase, the utility of specific pharmacological interventions in modifying outcome will be evaluated. The exploratory aspect of this approach is the extent to which it might suggest methods to improve decomposition of the relevant factors in human samples.

TITLE: Alcohol, HIV Risk Behaviors, and Sexual Victimization NIAAA
P.I.: Maria Testa, Ph.D.
INSTITUTION: Research Institute on Addictions, Buffalo, NY
GRANT NO.: 5R01AA12013-05
KEYWORDS: risk behaviors, HIV, sexual victimization, STDs, behavior
TYPE STUDY: Clinical
AMOUNT: $50,000

This application suggests that childhood sexual abuse and risk-prone personality (high sensation-seeking, high negative affect, low assertiveness) lead women to engage in risky behaviors (heavy alcohol and drug use, high levels of sexual activity and exposure to risky settings such as bars) which in turn increase the likelihood of experiencing both sexual victimization and HIV/STD infections. There will be a three wave cross-legged panel design using a representative sample of 1,000 unmarried women, ages 18-30, recruited from random digit dialing.

TITLE: Gender/Sex Differences in Stimulant Action NIDA
P.I.: Cynthia M. Kuhn, Ph.D.
INSTITUTION: Duke University Medical Center, Durham, NC
GRANT NO.: 2R01DA009079-08A1
KEYWORDS: sex differences, cocaine dependence, gonadal steroids, estrogen, dopamine
TYPE STUDY: Basic
AMOUNT: $296,133

Women comprise about one third of cocaine addicts. They start using cocaine earlier in life, are more sensitive to some cocaine effects and progress to dependence more rapidly. Rodents show some similarities to this pattern: cocaine elicits greater increases in cocain-stimulated locomotion, females work harder for cocaine reinforcement and extracellular dopamine rises more than in male rats. Our preliminary findings suggest that developmental exposures to gonadal steroids contributes to sex difference in cocaine action. The purpose of this proposal is to investigate the basis for the organizational effect of gonadal steroids on forbrain dopamine systems and the behavioral response to psychomotor stimulants mediated by these systems. The investigators will test the hypothesis that sex differences in cocaine effects reflect anatomical or functional differences in dopamine neurons established during ontogeny. To determine when steroid effects are exerted, male and female rats will be gonadectomized on postnatal day 2, prepubertally on day 25 or in adulthood, and cocaine-stimulated locomotion and electrically-stimulated dopamine overflow will be determined on postnatal day 70. To evaluate which steroids mediates these effects, rat pups will be treated with vehicle, testosterone or estrogen antagonists ICI82780 (females), and aromatase inhibitor or androgen antagonist flutamide (males) during the early postnatal window or during puberty and the same dependent measures will be assessed. Finally, to evaluate how organizational effects of steroids are manifested, the number of dopamine neurons, density of innervation, dopamine content and electrically-stimulated dopamine release in nucleus accumbens and caudate nucleus will be determined following the same treatments. These studies should provide insight into potential biologic mechanisms that influence gender differences in disease related to dopamine neuron function in humans including Parkinson's disease and psychostimulant addiction.

TITLE: Timing of Social Service Events on Women's Recovery from Drug Addiction NIDA
P.I.: Cathleen A. Lewandowksi, Ph.D.
INSTITUTION: Wichita State University (School of Social Work)
GRANT NO.: 1R03DA014360-01A1
KEYWORDS: drug treatment outcomes, drug-free, residential drug treatment, Life History Calendars
TYPE STUDY: Basic
AMOUNT: $73,000

The objective of this exploratory study is to develop and understand the impact of a multiple agency service delivery environment on women's drug treatment outcomes. This exploratory study has three specific aims: to assess the impact of a multiple agency service delivery environment on women's drug treatment outcomes, to describe the characteristics of women in recovery who receive services simultaneously or sequentially from multiple agencies, and to describe the multiple agency service delivery pattern over a one-year period. The main goal of this study is to lay the groundwork for future studies where more specific hypotheses can be tested. The research design is a longitudinal panel design, where services and drug recovery outcomes for women are examined, using both retrospective data and data collected over a 15-month data collection period. The following drug treatment outcomes will be examined: drug-free at end of study, drug recovery days, completion of treatment phases, employment/school, and reunification with biological children. Research will be conducted at a women's residential drug treatment program in Wichita, Kansas. Women who are admitted to the facility for drug treatment during a nine-month window (135) will be invited to participate. Primary data will be collected using structured interviews and Life History Calendars. These data collection instruments will be pilot-tested prior to the study's implementation. The initial structured interview will collect retrospective data on critical incidents occurring in women's lives

to that point. Life History Calendars will be used to collect more detailed information on service delivery patterns during the initial three months of treatment and to pinpoint the dates of critical events occurring the three months prior to treatment. Secondary data will be collected from the agency's database and case records. Univariate and bivariate statistics will be used to describe characteristics of this population and to examine women's perceptions of the multiple agency service environments. Multivariate data analysis will proceed using event history analysis to examine associations between key variables. Both continuous time and discrete time survival analysis will be used to investigate drug treatment outcomes. As the study is exploratory, differences in outcome cannot be necessarily attributed to treatment differences. Instead, interpretation of findings will suggest directions for subsequent studies.

TITLE: Women with Schizophrenia & Co-Occurring Substance Use Disorders NIDA
P.I.: Jean Gearon, Ph.D.
INSTITUTION: University of Maryland, MD
GRANT NO.: 5R29DA011199-05
KEYWORDS: schizophrenia, substance abuse, co-occurring substance use, HIV, risk factors, mental health
TYPE STUDY: Clinical
AMOUNT: $20,000

The primary goals of this project are: 1) to determine if women with schizophrenia and co-occurring substance use disorders are more vulnerable to HIV (e.g., engage in more high risk behaviors) and violent victimization than either women with major depression and co-occurring substance use disorders or women with substance use disorders only and no history of serious and persistent mental illness; 2) to determine if women with schizophrenia who abuse substances experience more violent victimization than women with major depression and co-occurring substance use disorders, or women with substance abuse disorders alone and no history of serious and persistent mental illness, and 3) to examine the causal sequencing between cognitive functioning, social competency, negative symptoms and HIV risk and victimization.

TITLE: Sexual Identity and Drinking: Risk and Protect Factors NIAAA
P.I.: Tonda L. Hughes, Ph.D.
INSTITUTION: University of Illinois at Chicago, IL
GRANT NO.: 5K01AA00266-04
KEYWORDS: Alcohol, lesbians, substance abuse, behavior
TYPE STUDY: Clinical
AMOUNT: $44,007

This study will use an existing survey instrument to examine and compare risk and protective factors for heavy drinking and alcohol-related problems in lesbians and heterosexual women. The study will include data from 600 women who are 18 years of age or older.

CANCER

TITLE: Clinical Trials of Two Human Papillomavirus (HPV)-like Particle Vaccines NCI
P.I.: Douglas R. Lowy, M.D.
INSTITUTION: NCI, Bethesda, MD
GRANT NO.: 1Z01BC09052
KEYWORDS: human papillomavirus, cancer, cervical, vaccine development, STDs
TYPE STUDY: Clinical
AMOUNT: $600,000

This project will perform the early phase clinical trials of two HPV16-based papillomavirus vaccines. L1 is a major structural papilloma viral protein that can self-assemble into virus-like particles (VLPs). It is thought that L1 VLP will only protect by preventing primary infection. To add another level of protection, a chimeric VLP was developed by adding the L2 minor capsid protein to the L1. After preclinical vaccine results, an early phase human trial of L1 HPV16 VLP vaccine is being tested. There are four groups of 12 normal volunteers 18-29 years old. In each group, ten volunteers received the vaccine and two received a placebo in a double-blind fashion.

TITLE: Mitotic Checkpoint & Genomic Stability in Ovarian Cancer FIC
P.I.: Dong-Yan Jin, Ph.D., M.D.
INSTITUTION: University of Hong Kong
GRANT NO.: 1R01TW006186-01
KEYWORDS: ovarian cancer, genomic instability, mitosia
TYPE STUDY: Basic
AMOUNT: $17,500

Ovarian cancer is a major cause of cancer death in women worldwide, but the molecular mechanisms of its pathogenesis are not known. The applicant has found that mitotic checkpoint defects are common in ovarian cancer cell lines. The proposed studies are designed to investigate the molecular basis of mitotic checkpoint in mammalian cells and its relevance to genomic instability in ovarian cancers. The hypothesis is that mitotic checkpoint genes are defective in ovarian cancers leading to genetic instability and, thus, contribute to the pathogenesis of this cancer.

TITLE: Tumor progression and apoptosis in mouse mammary gland FIC
P.I.: Edith C. Kordon, Ph.D.
INSTITUTION: Instituto de Investigaciones Hematologicas (IHEMA) Argentina
GRANT NO.: 1R01TW006212-01
KEYWORDS: apoptosis, breast cancer, hormones
TYPE STUDY: Basic
AMOUNT: $17,500

The project addresses two main goals: discovering new pathways involved in mammary tumor progression, particularly those related to the loss of hormone-dependency; and determine the events that initiate the cascades that trigger programmed mammary cell death during mammary gland involution. Understanding what determines the neoplastic-cell lack of response to the regulatory controls for cell proliferation and death is the main goal for experimental oncology. In the case of mammary cells, one of the main controls for proliferation and differentiation resides in the action of pregnancy-related hormones. Determine new genes and pathways that release the mammary epithelial cells from such a control is a fundamental issue in the fight against breast cancer.

TITLE: Acrogranin Function in the Ovary FIC
P.I.: Laura Diaz-Cueto, M.D., Ph.D.
INSTITUTION: Coordinacion de Investigacion en Salud IMSS
GRANT NO.: 1R01TW006189-01
KEYWORDS: ovarian cancer, growth factor, signal transduction
TYPE STUDY: Translational
AMOUNT: $17,500

Ovarian carcinoma is the fifth most common cause of cancer among women in the USA, with more than 23,000 new cases diagnosed and approximately 14,000 deaths each year. In Mexico, ovarian cancer is the seventh cause of cancer among women. Recent studies have demonstrated that a new family of growth factors [epithelin, granulins and acrogranin (the precursor)] have regulatory activities on preimplantation mouse embryo, normal epithelial and tumoral cells in rodents and human, following interesting signal transduction pathways and are over expressed in some kind of human cerebral tumors, renal cell epithelial carcinomas.

TITLE: Ethnicity Based Proteomic Biomarkers in Breast Cancer NCI
P.I.: Helena R. Chang, M.D.
INSTITUTION: University of California, LA
GRANT NO.: 1R01CA093736-01A1
KEYWORDS: African-American, biomarkers, breast cancer
TYPE STUDY: Basic
AMOUNT: $100,000

African American women are more likely found at advanced stage and therefore have a worse survival. While the poor outcome observed in African-American women with breast cancer may be multifactorial, the aggressiveness of their disease may have a biological base. A significant tumor shrinkage induced by preoperative chemotherapy may be used as a surrogate marker to predict patient's survival outcome. This study will search for novel specific proteins in breast cancer that predict tumor responses to preoperative chemotherapy. The chemical identities of these proteins will be determined by mass spectrometry/proteomics. In addition, whether the "drug-resistant" biomarkers are more common in African-American women will be systematically compared with the Caucasian American women. Finally, the prognostic value of the biomarkers will be compared with the conventional parameters such as patients' demographic and tumor features in a multivariant analysis to determine their independent predicative value and interaction of various factors.

CARDIOVASCULAR DISEASE

TITLE: Why is Cardiac Risk Increased in Rheumatoid Arthritis NIAMS
P.I.: Daniel H. Solomon, M.D., MPH
INSTITUTION: Brigham and Women's Hospital, Boston, MA
GRANT NO.: 1R03AR048264-01
KEYWORDS: rheumatoid arthritis, autoimmune disease, cardiovascular disease, myocardial infarction, atherosclerosis, Medicare/Medicaid, community-based
TYPE STUDY: Clinical
AMOUNT: $100,000

While rheumatoid arthritis is primarily considered a condition affecting the joints and impairing function, past data suggest that cardiac disease represents the number one cause of mortality in rheumatoid arthritis. However, the adjusted rates of cardiovascular death and myocardial infarction in rheumatoid arthritis are poorly characterized. Additionally, whether the increased cardiovascular risk is because of the medications used for rheumatoid arthritis or the underlying disease severity is unknown. The proposed research has two major aims: 1)to quantify the rates of cardiovascular death and myocardinal infarction in patients with rheumatoid arthritis after controlling for known cardiovascular risk factors, and 2) to determine the contribution of rheumatoid arthritis medication exposure and disease severity to cardiovascular disease rates. Prior work on this issue has largely been conducted in referral populations and attempts to control for known cardiovascular risk

factors have been poor. This issue will be studied in a large Medicare/Medicaid database that the investigators have extensive experience working with. This database contains information on over 2 million patients followed for 10 years and includes diagnosis and procedures for all physicians and inpatient visits. In addition, prescription data from a large pharmacy benefits program has been integrated into this database allowing for a complete characterization of an individual patient's medication exposure. While any one diagnosis of rheumatoid arthritis may not be accurate in such a database, the project entails a validation sub-study to develop an algorithm for selecting patients with a high probability of having rheumatoid arthritis. The proposed project will be an important advance in this area because of the large number of patients with rheumatoid arthritis to be included (over 5,000), the community-based nature of their care, the ability to control for known cardiovascular risk factors, the extensive medication information allowing for us to explore key hypotheses regarding corticosteroid exposure, and the attempt to simultaneously control for disease severity.

TITLE: Cardiovascular Risk in Former Gestational Diabetic Women NINR
P.I.: Kathleen B. King, Ph.D.
INSTITUTION: University of Rochester
GRANT NO.: 1R01NR007659-01A1
KEYWORDS: cardiovascular disease, gestational diabetes mellitus (GDM), risk factor profile, serum lipids, blood pressure, insulin sensitivity, central obesity, BMI
TYPE STUDY: Clinical
AMOUNT: $100,000

The association between diabetes and risk for cardiovascular disease is well established. Women with a history of gestational diabetes mellitus (GDM) are at increased risk of developing type 2 diabetes later in life, and limited but suggestive evidence demonstrates that these women also are more likely to have an unfavorable risk factor profile for coronary heart disease (CHD). The primary aim of this project is to examine the prevalence of risk factors for CHD in women with a history of GDM compared to women without a history of GDM. The investigators will test whether women with a history of GDM: 1) have a higher calculated 10-year relative risk for CHD, 2) have more adverse levels of individual risk factors for CHD, and 3) are more likely to develop CHD risk factors at a younger age, compared to women who did not have GDM, controlling for body size. The secondary aim of this project is to evaluate women's perceptions of their future risk of developing both CHD and diabetes, and whether perception of risk is related to the actual risk. Eighty women with a history of GDM (cases) and 80 women without a history of GDM (controls), who were 30 years of age or older when they gave birth and are now 5 to 10 years postpartum, will be recruited. Cases and controls will be matched for age, ethnicity, and body mass index (BMI) within year of the index pregnancy. Data will be collected during an outpatient admission to the NIH funded General Clinical Research Center. The primary outcomes will calculate relative risk of CHD, serum lipids, blood pressure, and insulin sensitivity. The secondary outcomes will be perception of risk for diabetes and CHD. Body size will be control by matching on pre-pregnancy BMI, as well as controlling for current BMI, and central obesity. Demographic and clinical variables, in particular variables known to be related to CHD and/or distributed differently among cases and controls will be considered for inclusion as control variables prior to hypothesis testing. Regression and logistic regression analysis will be used to test for differences between women with and without GDM on the study outcomes. Correlational analysis will be used to determine the relationship between perception and actual risk.

DIABETES

TITLE: The Post-Diabetes Prevention Program Follow-up Study NIDDK
P.I.: Sarah Fowler, Ph.D.
INSTITUTION: George Washington University
GRANT NO.: 2U01DK048489-10
KEYWORDS: diabetes, cardiovascular disease, minority populations, elderly, gestational diabetes
TYPE STUDY: Clinical
AMOUNT: $300,000

The Diabetes Prevention Program is a multi-center controlled clinical trial examining the efficacy of an intensive life-style intervention or metformin to prevent or delay the development of diabetes in a population selected to be at high risk due to the presence of impaired glucose tolerance (IGT). Development of diabetes, defined by 1997 ADA criteria, is the primary outcome while cardiovascular disease and its risk factors are important secondary outcomes. The DPP began recruitment in mid-1996. At the time of this application, total study exposure is a mean of *3.4 years (range 2.4 to 5.4) with a total of *10,000 patient years in the 3,234 volunteers in the 3-arm study. On the basis of a statistically significant and clinically compelling decrease in the development of diabetes in the life-style intervention and metformin-treated groups (58% and 31% risk reductions, respectively) compared with the placebo treated group, the DPP Data Monitoring Board and NIDDK ended the masked treatment phase of the study in May, 2001, one year earlier than originally planned. This research is designed to take further advantage of the scientifically and clinically valuable cohort of DPP volunteers and the large volume of data collected during the study. The highly compliant DPP cohort, including 45% minorities, is the largest IGT population ever studied. Moreover, the sub-cohort that has developed diabetes (n*700) has been followed from near the exact time of diabetes onset. Clinically important research questions remain in the wake of the DPP. The carefully collected, centrally measured and graded data in this cohort should help to answer, definitively, a number of important questions regarding the clinical course of IGT and early onset type 2 diabetes. Specific aims include: 1) Examine the long-term effects and durability of prior DPP intervention on the major DPP outcomes including diabetes, clinical cardiovascular

disease, atherosclerosis, CVD risk factors, quality of life and cost-benefit; 2) Determine the clinical course of new onset type 2 diabetes and IGT, in particular regarding microvascular and neurologic complications; 3) Determine the incidence of cardiovascular disease (CVD), CVD risk factors and atherosclerosis in new onset type 2 diabetes and IGT; and 4) Examine topics 1-3 in minority populations, men vs. women, and in older subjects in the DPP.

TITLE: Diabetes Prevention Program (DPP) NIDDK
Primary Prevention Program - Data Coordinating Center
P.I.: Sarah Fowler, Ph.D.
INSTITUTION: George Washington University
GRANT NO.: 5U01DK048489-08
KEYWORDS: diabetes, non-insulin dependent diabetes mellitus, impaired glucose tolerance, prevention
TYPE STUDY: Clinical
AMOUNT: $67,500

The Diabetes Prevention Program (DPP) is a multi-centered randomized trial designed to determine whether type 2 diabetes can be prevented or delayed in a population of high-risk individuals. Included in the high-risk population are women with a history of GDM and individuals with impaired glucose tolerance. There are 3.234 participants enrolled in the three-arm study with two active treatment groups (metformin and life-style) compared to placebo controls. Of the total recruited, 68% were women, 13% of these had a history of GDM, and nearly 50% were from minority populations.

TITLE: Diabetes Prevention Program (DPP) Primary Prevention Trial NIDDK
P.I.: David Marrero, Ph.D.
INSTITUTION: Indiana Univ-Perdue University at Indianapolis, Indianapolis, IN
GRANT NO.: 5U01DK048406-09
KEYWORDS: diabetes, behavior modification, prevention, gestational diabetes mellitus, weight control, clinical trials
TYPE STUDY: Clinical
AMOUNT: $67,500

The primary goal of the proposed project is to determine, via a collaborative multicenter trial, whether interventions can: a) prevent persons with impaired glucose tolerance (IGT) or a history of gestational diabetes mellitus (GDM) from developing non-insulin-dependent diabetes mellitus (NIDDM); and b) prevent the worsening of glucose tolerance in people with newly diagnosed NIDDM. Because of the ethnic diversity of the study populations, a secondary goal is to design the interventions to be sensitive to varying social, ethnic, and cultural values. With the use of the Regenstrief Medical Record System, we have identified three potential high risk populations: a) 6721 persons with a prior history of diabetes with random blood glucose values of 108-160 mg/dl and concomitant risk factors for NIDDM, of whom 54% are African-American, b) 3688 patients with NIDDM in whom we will contact their first degree relatives, and c) between 530-600 women with a history of GDM projected to be available by enrollment, 34% of whom are African-American. We plan to evaluate, using a randomized control group comparison design, the relative effectiveness of the proposed interventions in reducing conversion to NIDDM in persons with IGT, and deterioration of glucose tolerance in newly diagnosed NIDDMs as primary end points and macrovascular risk glucose tolerance in newly diagnosed NIDDMs as primary end points and macrovascular risk factors, coronary events, and overall mortality as secondary end points.

TITLE: Diabetes Prevention Program (DPP) NIDDK
P.I.: Harry Shamoon, M.D.
INSTITUTION: Yeshiva University, New York, NY
GRANT NO.: 5U01DK048349-09
KEYWORDS: diabetes, prevention, gestational diabetes mellitus, weight control, clinical trials
TYPE STUDY: Clinical
AMOUNT: $21,000

By selecting populations at higher than average risk for the ultimate development of NIDDM, the Diabetes Center at the Albert Einstein College of Medicine will test the following hypothesis: The reduction in risk of developing NIDDM in persons at high risk for the development of diabetes will be dependent on treatment which affects insulin resistance, islet B-cell dysfunction, and/or hepatic glucose production. Interventions which include diet, exercise sulfonylurea drugs, and metformin in a factorial design can address this hypothesis. The Albert Einstein Center has a large, identified population of individuals from racial and ethnic minority groups in the Bronx and Westchester Counties who receive their medical care in Einstein-affiliated programs; an identified and well characterized population of women who had gestational diabetes diagnosed between 1988 and the present, and an annual accrual of an additional cohort of women with gestational diabetes; members of the treatment team with specific competence in diabetes in Hispanic and in African-American individuals; expertise in related areas such as hypertension control, cardiovascular risk reduction, and behavioral techniques intended to achieve therapeutic goals.

TITLE: NIDDM Primary Prevention Trial (DPT-2) NIDDK
P.I.: Neil White, M.D.
INSTITUTION: Washington University, St. Louis, MO
GRANT NO.: 5U01DK048400-09
KEYWORDS: diabetes, gestational diabetes mellitus, prevention, clinical trial
TYPE STUDY: Clinical
AMOUNT: $22,000

The proposed intervention is centered on an intensive, multi-disciplinary, program to promote long-term weight loss and increase physical activity among 200 volunteers who work in or live near the Washington University Medical Center in St. Louis. The proposed intervention is designed to minimize physical discomfort and life style disruption, to emphasize gradual, moderate changes in the foods usually eaten, to maximize continued adherence over five years and to be acceptable to both white and African-American volunteers. In order to sustain this weight loss long term, it is proposed to have the intensively managed patients seen regularly by trained members of a multidisciplinary team that will consist of an exercise technician, a nutritionist, a nurse, and a social worker trained in behavioral medicine. Volunteers randomized to the control group will be seen quarterly and provided with state of the art educational and motivational materials that will include recommendations for weight loss, increase physical activity aid a prudent diet low in saturated fats and cholesterol.

TITLE: Diabetes Prevention Program (DPP) NIDDK
P.I.: Janet A. Tobian, M.D.
INSTITUTION: University of Chicago, Chicago, IL
GRANT NO.: 5U01DK048381-09
KEYWORDS: diabetes, prevention, clinical trials
TYPE STUDY: Clinical
AMOUNT: $22,000

This grant is multi-center trial in which subjects would be screened for inclusion and exclusion criteria. A primary prevention subgroup will consist of subjects with impaired glucose tolerance (IGT) by National Diabetes Data Group (NDDG) criteria with a fasting plasma glucose (FPG) equal to or more than 110 mg/dl. A secondary intervention subgroup will consist of individuals with NIDDM by NDDG criteria and a FPG g 140 mg/dl. The subjects will be randomized in a 2 x 2 factorial design to: 1) intensive program of diet, exercise and stress reduction versus standard dietary and exercise advice as well as 2) therapy with either glipizide or placebo. We propose that the diet/exercise intervention be modeled after the PATHWAYS program (diet, exercise and stress management) which has been validated as an effective method of weight reduction in inner city African-American women. Individuals will be followed to test whether these interventions can: 1) prevent the worsening of glucose tolerance in these subjects over 5 years and 2) reduce cardiovascular morbidity and mortality.

ENDOCRINOLOGY

TITLE: Plasticity of Hypothalamic Neurons: Estrogen Effects NINDS
P.I.: Oline K. Ronnekleiv, Ph.D.
INSTITUTION: Oregon Health Science University
GRANT NO.: 2R01NS035944-05A1
KEYWORDS: neuroendocrine, hypothalamus, estrogen, gonadotropin releasing hormone (GnRH), plasticity
TYPE STUDY: Basic
AMOUNT: $100,000

The long-term objective of this research is to explore the biphasic effects of 17-beta-esttradiol (E2) on synaptic transmission that results in inhibition and subsequent activation of gonadotropin releasing hormone (GnRH) neurons. Preoptic (POA) GABA neurons that synapse on GnRH neurons are critical for mediating these effects of E2. The working hypothesis is that estrogen modulates the expression and function of ion channels and receptors in hypothalamic GABA neurons, which are involved in negative and positive feedback of GnRH release. The first experiments will explore the effects of estrogen on calcium T-channel activity in hypothalamic GABA neurons during negative and positive feedback. Tissues will be prepared from ovariectomized oil- and E2-treated animals. The mRNA expression of T-channel subunits will be measured using ribonuclease protection assay (RPA) and in situ hybridization. This expression will be correlated with T-channel activity in individual neurons using whole-cell patch recording and single-cell RT-PCR. Also, the effects of estrogen on the coupling of the GABA-B receptor in inhibition of I(t) will be measured using whole-cell recording. The second experiment will explore the effects of E2 on the expression of Katp channels in POA GABA neurons. The relative mRNA expression of the Katp subunits (Kir 6.2 nd SUR 1, 2) will be measured in the POA following estrogen using RPA and in situ hybridization. The responses to Katp channel openers and the effects of baclofen will be measured in GABA neurons using whole-cell recording, and the expression of Katp transcripts identified using RT-PCR. The third experiments will explore how E2 alters the coupling of the alphal-adrenergic and glutamate metabotropic receptors to SK channels in hypothalamic GABA neurons. The effects of estrogen on the SK current in GABA neurons will be measured using whole-cell recording and single cell RT-PCR. Also, the cellular pathways underlying the effects of E2 on the alphal-adrenergic inhibition of the SK current will be explored using whole-cell recording during negative and compared to positive feedback. Finally, the coupling of the glutamate metabotropic (mGluR1, GluR5) receptors to inhibition of SK channels in POA GABA neurons will

be explored using whole-cell recording, and the relative mRNA expression of mGluR1, GluR5 in GABA neurons determined using RT-PCR. These studies will provide important new information about the mechanisms by which E2 alters the excitability of POA GABA neurons during negative and positive feedback, and in general how estrogen modulates GABAergic synaptic activity in the mammalian brain.

EYE DISEASE

TITLE: Incidence of Late Macular Degeneration in Older Women — **NEI**
P.I.: Anne L. Coleman, M.D.
INSTITUTION: UCLA
GRANT NO.: 1U10EY13626-01A1
KEYWORDS: blindness, quality of life
TYPE STUDY: Epidemiologic (case-control)
AMOUNT: $230,000

Age-related macular degeneration is the number one cause of irreversible blindness in the United States and is more prevalent in older, Caucasian women. Although there have been several studies on the incidence of ARM, none of these studies has been able to provide accurate estimates on the incidence of late ARM and/or the progression of ARM in the oldest old, those individuals over 80 years of age, because of the limited sample sizes in these studies in this age group. The population in the Study of Osteoporotic Fractures (SOF) is an appropriate cohort in which to evaluate the incidence of late ARM and the progression of ARM, because the mean age of the women at the re-examination will be 84.4 years of age and the sample is mainly Caucasian. The proposed research study aims to determine the incidence of late ARM, the rate of progression of ARM, and the association of specific risk factors such as diabetes mellitus and prior cataract surgery with late ARM and the progression of ARM in elderly women. In addition, it aims to determine the trajectory of visual decline in older women over a 14- year period. Secondarily, it aims to determine the impact of late ARM on vision-targeted health-related quality of life and to determine whether or not an association exists between the progression of ARM and the risk of falling and hip/non-spine fractures. In 1997 to 1998 (Visit 6), 5482 women had an eye examination that consisted of a medical and ocular history, nine questions from the National Eye Institute Visual Function Questionnaire (NEI-VFQ), and measurements of visual acuity, contrast sensitivity, peripheral vision with automated perimetry, intraocular pressure, and uncorrected refractive error. These women also had a refraction and imaging of their lenses and fundi of both eyes through dilated pupils. Approximately 4.5% of these women have photographically validated late ARM, 41.5% have early ARM, and 54% have no ARM or hard drusen only. In the proposed re-examination, we will update their medical and ocular history and ask them the nine questions from the NEIVFQ. In addition, visual acuity and contrast sensitivity will be re-measured. Fundus photographs of both eyes through dilated pupils will be obtained. These photographs and the relevant photographs from 1997 to 1998 will be graded for ARM with the Wisconsin Age-Related Maculopathy Grading System (WARMGS) in a masked fashion so that the readers do not know which film is from which visit. The University of Wisconsin will also grade the fundus photographs on 30% of the eyes with ARM and 10% of the total sample. This will allow the identification of women in SOF who have had progression of their ARM and developed late ARM since 1997 and 1998.

TITLE: Visual Dysfunction and Quality of Life in Multiple Sclerosis — **NEI**
P.I.: Laura J. Balcer, M.D.
INSTITUTION: University of Pennsylvania, Philadelphia, PA
GRANT NO.: 1R01EY13273-02
KEYWORDS: visual impairment, Quality of Life, Multiple Sclerosis, autoimmunity, behavior
TYPE STUDY: Cohort Study
AMOUNT: $125,000

Visual impairment is a leading cause of symptoms in patients with multiple sclerosis (MS). The extent to which vision has been affected by new therapies for MS is not known, and has been difficult to assess using traditional measures of neurologic impairment. The visual profile of MS has not been examined, and the relation of visual function to overall neurologic impairment in patients with MS has not been determined in a large, heterogeneous cohort. This proposal will accomplish the following specific aims: 1. Define the visual profile of MS in a large cohort (400 patients), and determine which measures best identify visual dysfunction in patients with MS; and 2. Determine the relation of visual function to vision- and disease-specific HRQOL in patients with MS.

GASTROENTEROLOGY

TITLE: Cognitive Therapy as a Treatment for Irritable Bowel Syndrome (IBS) — **NIDDK**
P.I.: Edward Blanchard, Ph.D.
INSTITUTION: State University of New York, Albany, NY
GRANT NO.: 5R01DK54211-04
KEYWORDS: Irritable bowel syndrome, cognitive therapy, mental health, behavior
TYPE STUDY: Clinical
AMOUNT: $100,000

Recent research suggests that cognitive therapy (CT) is highly effective (70-80% clinically improved) in the short-term (3 months) as a treatment for IBS. This application seeks to replicate and extend previous small-scale studies by conducting a

controlled clinical trial of CT vs. a self-help support group as an attention placebo control and follow-up of the treated patients for at least 12 months.

TITLE: Biofeedback for Fecal Incontinence and Constipation — NIDDK
P.I.: William E. Whitehead, Ph.D.
INSTITUTION: University of North Carolina, Chapel Hill, NC
GRANT NO.: 3R01DK57048-03
KEYWORDS: Biofeedback, fecal incontinence, constipation, pelvic floor dyssynergia, behavior
TYPE STUDY: Clinical
AMOUNT: $75,000

Among constipation patients, half are reported to have pelvic floor dyssynergia, a condition marked by an inability to relax pelvis floor muscles during evacuation. Biofeedback has been recommended for the treatment of both conditions because uncontrolled studies over the past 10-25 years suggest that these treatments are as effective as medical or surgical management and involve no risk. However, placebo-controlled trials are lacking in this area. The aims of the proposed research are: 1) to compare biofeedback to alternative therapies for which patients have a similar expectation of benefit; 2) to identify which patients are most likely to benefit; and 3) to assess the impact of treatment on quality of life. Two long-term, prospective, single-blind studies will be conducted. Study I will compare biofeedback for the treatment of fecal incontinence to a standard therapy, Kegel exercises. Study II will compare biofeedback for pelvic floor dyssynergia to a skeletal muscle relaxant drug (diazepam) and to placebo medication. These studies will help to establish the efficacy of biofeedback on the treatment of defecatory disorders.

GENITOURINARY

TITLE: Balkan Nephropathy: Environmental/Clinical Epidemiology — FIC
P.I.: Palmen S. Dimitrov, M.D.
INSTITUTION: National Center of Hygiene, Medical Ecology & Nutrition, Bulgaria
GRANT NO.: 1R01TW006192-01
KEYWORDS: epidemiology, nephrology
TYPE STUDY: Epidemiologic (case-control)
AMOUNT: $17,500

This project is designed to identify the earliest stages of Balkan Endemic Nephropathy (BEN) by following up offspring of BEN cases and controls drawn from a previous study of this disorder in Bulgaria. BEN is a chronic kidney disease of unknown etiology, although it shows both familial and geographic aggregation. The strong familial aggregation seen in this disorder does raise the possibility of genetic components to this disease. Although its causes are not well understood and its geographical range is thought to be limited, it is a significant cause of morbidity and mortality in rural Bulgarian populations. This disease could reveal important physiologic components common to other kidney diseases, as well.

HIV/AIDS

TITLE: Haiti Comprehensive AIDS/TB Research Training (PA02-022) Phase I – ICOHRTA – AIDS & TB Grant Programs — FIC
P.I.: Jean W. Pape, M.D.
INSTITUTION: Gheskio Centers, Haiti
GRANT NO.: 1R21TW006151-01
KEYWORDS: HIV prevention and treatment clinical trials, STDs
TYPE STUDY: Clinical, training and capacity building
AMOUNT: $20,000

This proposal is for the GHESKIO Centers in Port au Prince Haiti to prepare for the ICOHRTA-AIDS/TB program. The GHESKIO Centers is a Haitian non-governmental research and training organization working in close partnership with the Haitian Government on HIV and inter-related diseases such as tuberculosis and sexually transmitted infections. The research base for the ICOHRTA-AIDS/TB program in Haiti will be 1) HIV prevention clinical trials of HIV vaccines and vaginal microbicides through the NIH HVTN and HPTN. 2) Therapeutic clinical trials for adults and children of highly active antiretroviral therapy (HAART) regimens and tuberculosis regimens 3) Operational and health science research in support of an expansion of GHESKIO service activities to 25 departmental health centers in Haiti. This expansion is being supported by the Haitian MOH, the United States Agency for International Development, and Mission of French Cooperation.

TITLE: Natal-Columbia Clinical AIDS/TB Training Program (PA02-022) Phase I – ICOHRTA – AIDS & TB Grant Programs — FIC
P.I.: Salim S. Abdool Karim, M.D., Ph.D.
INSTITUTION: University of Natal, South Africa
GRANT NO.: 1R21TW006111-01
KEYWORDS: HIV/AIDS, tuberculosis, infectious diseases
TYPE STUDY: Clinical, training capacity building
AMOUNT: $20,000

South Africa is currently experiencing one of the worst H IV epidemics in the world and tuberculosis is the most common opportunistic infection associated with advancing HIV disease and AIDS. The recent, substantial increase in numbers of people co- infected with HIV and tuberculosis is exacerbating the existing tuberculosis crisis in South Africa. Building on longstanding collaborative relationships, a collaborative program in clinical, operational and health services research and training will be developed to fill an important training gap in the local response to the HIV and tuberculosis epidemics in South Africa. The continuum of training concept that has evolved through Fogarty AITRP for HIV and tuberculosis basic science, public health, behavioral and ethics research training where Fellows do coursework in the US and conduct their research in South Africa will be applied to this proposed training program for building clinical, operational and health services research capacity.

TITLE: AIDS and TB Training Opportunities Program (ATTOP) FIC
(PA02-022) Phase I – ICOHRTA – AIDS & TB Grant Programs
P.I.: Peter N. Mugyenyi, DCH, MRCP
INSTITUTION: Joint Clinical Research Center, Uganda
GRANT NO.: 1R21TW006117-01
KEYWORDS: HIV/AIDS, tuberculosis
TYPE STUDY: Clinical, training, capacity building
AMOUNT: $10,000

Although the seroprevalence of HIV has declined in Uganda over the past 10 years, the HIV epidemic in Uganda is far from controlled. In the face of the HIV epidemic, tuberculosis rates are high and associated with significant mortality. With the advent of antiretroviral therapy, prevention strategies alone are no longer sufficient to meet the current needs in Uganda. One key step in the rebuilding of the Ugandan public health infrastructure resulted from a unique collaboration between the Ugandan Ministry of Health, the Ministry of Defense and Makerere University to form the Joint Clinical Research Center (JCRC). The JCRC is a research and health care facility devoted entirely to HIV and leads the way in opening Africa to antiretroviral therapy. The goal of this proposal is to develop a comprehensive training program that will build the Ugandan capacity to translate basic and clinical research findings into public health policy and interventions. The training program will build on a growing number of clinical research projects on HIV and TB and extend the findings of these studies to the public health and policy arena.

TITLE: AIDS and TB Research Training Program for Botswana FIC
(PA02-022) Phase I – ICOHRTA – AIDS & TB Grant Programs
P.I.: Sheila D. Tlou, Ph.D.
INSTITUTION: University of Botswana
GRANT NO.: 1R21TW006101-01
KEYWORDS: HIV/AIDS, tuberculosis
TYPE STUDY: Clinical, training, capacity building
AMOUNT: $20,000

With an HIV prevalence rate of 38.5 percent among adults aged 15 to 49, the most economically productive age group, and a shortage of health care providers equipped to provide AIDS care, Botswana is experiencing an economic and public health crisis. In
addition, despite a successful tuberculosis prevention program, particularly regarding the prevention of tuberculosis among those who are HIV positive, tuberculosis is responsible for 20 percent of all hospital admissions and 20 percent of adult deaths in Botswana. While the spread of these diseases offer a challenging future for the country, Botswana is committed to supporting research and interventions aimed at halting these epidemics and caring for those affected. As Botswana undertakes efforts to advance comprehensive responses to the AIDS epidemic- such as providing antiretroviral therapy and establishing new education and outreach programs-developing means by which scientific and operational research capacity increases is critical. Data gathered from such efforts will have important implications for improving care, creating effective prevention methods, and designing better public health programs and policies. Therefore, the development of training programs for those who are to be engaged in clinical, operational, and health services research must be carefully developed so as to build upon Botswana's expertise and to offer new opportunities for those in need of additional information and training. Through this proposal, we will develop a comprehensive research training plan for HIV, AIDS, and tuberculosis in Botswana that meets the specific needs of the country and region, ensures long-term sustainability, and fosters collaboration with other organizations and individuals working within the country.

TITLE: Planning for Chinese HIV Prevention Training Program FIC
(PA02-022) Phase I – ICOHRTA – AIDS & TB Grant Programs
P.I.: Zunyou Wu, M.D., Ph.D.
INSTITUTION: National Center for AIDS Prevention and Control, China
GRANT NO.: 1R21TW006094-01
KEYWORDS: HIV/AIDS, public health assessment
TYPE STUDY: training, capacity building
AMOUNT: $10,000

The Chinese Center for Disease Control and Prevention (China-CDC) will plan a comprehensive training program for HIV/AIDS prevention and treatment for China (China-ICOHRT A). The objectives of the one-year planning proposal are: 1)

to identify priorities for China in training of health professionals and personnel on AIDS and TB by consulting officials from the Ministry of Health, public health officers, researchers, and clinicians from provincial and local health agencies and institutes in China; 2) to assess resources available for research training by visiting the collaborating American institutions with the results of the earlier needs assessment to appropriately explore the resources at each institution; 3)to develop a comprehensive training program based on priority and resources assessments. An assessment of China's needs and its own research resources will be carried out for producing a report and prioritizing the current needs of AIDS/HIV control and prevention in China.

TITLE: Typology of Street Prostitutes: HIV Risk & Well-Being NIDA
P.I.: Celia Williamson, Ph.D.
INSTITUTION: University of Toledo
GRANT NO.: 1R03DA014999-01A1
KEYWORDS: HIV, STD, drug abuse, violence, victimization, prostitute, risk factors
TYPE STUDY: Clinical
AMOUNT: $71,000

The overall aim of the proposed qualitative grounded theory research project is to identify the types of prostitutes involved in street level prostitution. This will be accomplished over a 2-year period by attending to the specific aims of the project which are 1) to examine and verify the existence of various behavioral types of street level prostitutes, 2) to examine the moderating and mediating factors associated with well-being and risk. 3) To examine how the "type" affects women's involvement with 4 common risk factors associated with street level prostitution namely, HIV, violence, drug abuse, and emotional and physical well-being. 4) To examine the lifestyle of each type of female street level prostitute. 5) To determine the factors that contribute to women initially becoming a particular type of street level prostitute or shifting to another "type" within the range of street level prostitution. This study is a validation study to verify what was found in a preliminary qualitative study of 21 women from the Midwest. A typology of street level prostitutes, namely, Conventional Pimp Controlled, Renegade, and Outlaw Prostitutes were found in the preliminary study. The proposed study will take place in Midwestern State of Ohio. 45 women will be involved including 15 Conventional Pimp Controlled, 15 Renegade, and 15 Outlaw prostitutes. Of those 45, 15 will be interviewed in jail, 15 in social service programming, and 15 actively working. The study will fill an important gap in that a more complete knowledge base will be developed to provide important scientific data for planning future research on women's involvement in street level prostitution. This study is in preparation for a larger multiyear R01 study that will seek to determine the common pathways from entrance to exit for the categories of women involved in street level prostitution. The present proposal will also offer important practical insights on service-related barriers and provide helping professionals with the information needed to develop programming that is tailored to the needs of street level prostitutes in order to slow the speed of HIV and other prostitute-related risk factors.

TITLE: HIV-related oral disease among women in Harare FIC
P.I.: John S. Greenspan, BDS, Ph.D.
INSTITUTION: University of California, San Francisco
GRANT NO.: 1R03TW006054-01
KEYWORDS: HIV-infected, oral mucosal lesions, HIV disease progression, anti-retrovirals, immunologic marker
TYPE STUDY: Clinical
AMOUNT: $34,523

This research has focused on HIV-infected populations in the US. However, the investigators are proposing, as part of the present FIRCA application, to expand the study of the role and significance of oral manifestations of HIV infection to a setting that thus far has been understudied: sub-Saharan Africa. Because biologic assays to measure HIV disease progression are rarely accessible in sub-Saharan African countries due to prohibitive cost, other less expensive means of monitoring disease progression are needed. In US populations, visual inspection of the mouth and diagnosis of selected oral mucosal lesions have been found to be good predictors of HIV disease progression. If the predictive role of oral examination can be confirmed in sub-Saharan Africa, this would provide an important new tool for clinicians and public health specialists in this setting with respect to initiation of certain prophylactic drug regimens (such as tuberculosis or pneumocystis pneumonia prophylaxis) or anti-retrovirals. In collaboration with an investigator who is conducting a cross-sectional study among HIV-infected and non-infected women in Zimbabwe to estimate oral mucosal disease prevalence in relation to HIV serostatus in this population, this investigator is proposing to conduct a longitudinal study by expanding this ongoing cross-sectional study among Zimbabwean women. The objectives are 1) to estimate oral mucosal disease incidence in relation to a known immunologic marker of HIV disease progression (CD4 lymphocyte count); and 2) assess the sensitivity and specificity of detecting oral mucosal lesions by visual inspection of the mouth by trained nurses in a family planning/gynecology clinic in the sub-Saharan African setting. To address these objectives, the investigator will conduct follow-up oral examinations at 6-month intervals on 225 HIV-positive participants who are being recruited into a cross-sectional study from an ongoing parent cohort study. Each participant would be seen at 6-month intervals over a 3-year period as a part of the proposed study.

IMMUNITY/AUTOIMMUNITY

TITLE: Sex-based Differences in Anti-viral Immunity and SLE NIAID
P.I.: Sally R. Sarawar, Ph.D.
INSTITUTION: LaJolla Institute
GRANT NO.: 1R21AI51862-01
KEYWORDS: Lupus, autoimmunity, EBV, animal research
TYPE STUDY: Basic
AMOUNT: $50,000

SLE is a prevalent autoimmune disease with a significantly higher incidence in females than in males. Studies on the etiology of SLE indicate that both genetic and environmental factors influence disease penetrance. A strong correlation between SLE and previous infection with Epstein Barr virus (EBV), but not with other viruses has been reported. However, some studies have failed to find evidence of a viral etiology for SLE. This may be due to the high prevalence of EBV infection, unknown host/virus parameters, and the fact that multiple genetic loci control susceptibility to SLE. New Zealand mice are susceptible to SLE, and genetic loci that control disease susceptibility in these mice have been identified. C57/BL6 congenic mouse strains carrying one or more of three of the susceptibility loci designated SLE 1, 2, and 3 have been generated. It has been shown that the presence of at least two loci is necessary for high disease penetrance. We propose that a mouse viral homologue of EBV could substitute for the presence of a second locus, and could trigger disease in mice congenic for a single locus. We also suggest that this effect may differ in males and females, due, in part, to the more vigorous response to infection in the latter. We have a mouse model of gammaherpesvirus infection, which closely resembles EBV infection in humans and, like EBV, is able to induce non-specific B cell activation and autoantibody production, but does not induce overt autoimmune disease in C57BL/6 mice. In the present study, we will determine whether there are sex-based differences in the immune response to MHV-68 infection. We will determine whether infection of susceptible mice, bearing one or more SLE susceptibility locus, with MHV-68 can induce or exacerbate autoimmune disease and whether this effect differs in male and female mice. We will also determine whether there are genes whose expression is similarly modified by the presence of disease loci and the viral infection and whether their expression correlates with the induction of autoimmune disease.

TITLE: Mechanism Regulating Neutrophil Activation in Pregnancy NIAID
P.I.: Howard R. Petty, Ph.D.
INSTITUTION: Wayne State University
GRANT NO.: 1R01AI51789-01
KEYWORDS: autoimmunity, rheumatoid arthritis, pregnancy
TYPE STUDY: Translational
AMOUNT: $50,000

This grant will identify and characterize differences in the innate and adaptive immune response between genders, with a specific call for interdisciplinary clinical and basic research studies that may be important in the understanding and treatment of autoimmune diseases. Neutrophils are key cells in the development of homeostatic as well as pathologic inflammatory responses. These cells play a central role in the generation of tissue damage in autoimmune diseases (i.e., rheumatoid arthritis) as well as in infectious diseases, including sepsis. The studies outlined in this application are designed to study the differences in neutrophil function in non-pregnant women, pregnant women, and men. The study funding finding may offer a unique opportunity for the identification of endogenous mechanisms affecting women's health. Studying neutrophil biology during pregnancy will result in a mechanistic understanding of factors responsible for clinical improvement in certain autoimmune diseases during pregnancy and will also lead to the development of novel therapeutic approaches to control inflammation and autoimmunity.

TITLE: Sex-based Differences in the Immune Response NIAID
P.I.: Betty Diamond, M.D.
INSTITUTION: Albert Einstein College of Medicine
GRANT NO.: 1R01AI51767-01
KEYWORDS: autoimmunity, hormones, animal models
TYPE STUDY: Basic
AMOUNT: $50,000

The grant will undertake studies to investigate the effects of estradiol on the negative selection of naive autoreactive B cells in BALB/c and C57B1/6 mice. The goal of the study is to understand what genes and pathways are involved in estrogen-mediated B cell survival and B cell activation, and to understand what underlies an estrogen mediated breakdown in humoral self-tolerance. The 3 Specific Aims are: Aim 1, investigates the estradiol-induced alterations in marginal zone (MZ) B cell phenotype, function, and gene expression, and finally addresses B cell repertoire selection. Aim 2, addresses the role of estradiol in the generation of MZ B cells and the role of intracellular tyrosine kinase, Pyk-2, in the phenotype formation of these cells, and focuses on how estradiol rescues MZ B cells, and some potentially autoreactive B cells, in Pyk-2 deficient mice. Aim 3 will characterize estradiol-induced signaling pathways that may alter B cell repertoire selection in BALB/c versus C 57B1/6 mice, and will identify the cell type responsible for differential responsiveness to estradiol. The work should provide informative data about the survival of cells that may initiate an autoimmune response, and the role of

sexual dimorphism in this phenomenon.

TITLE: Genetics of Rheumatoid Arthritis NIAMS
P.I.: Peter Gregersen, M.D.
INSTITUTION: North Shore-Long Island Jewish Research Institute
GRANT NO.: N01AR22263
KEYWORDS: RA, genetics
TYPE STUDY: Genetics Consortium
AMOUNT: $250,000

The objective of this contract is the continuation of the North American Rheumatoid Arthritis Consortium (NARAC) along with a centralized repository of data, cells, and DNA of well-characterized RA pairs/pedigrees to advance the discovery of specific genes involved in the susceptibility and severity of rheumatoid arthritis. The Contractor will conduct research and generate resources based on the most current information about the likely chromosomal locations of these genes, as well as current knowledge about the underlying biology and pathophysiology of rheumatoid arthritis. The resources will generally consist of clinical information and biological materials on well-defined patient populations, as well as databases containing data on clinical phenotype, genotypes and other biomarkers. In order to maximize the utility of this resource, these databases and biological repositories will be designed to allow for future addition of new information, including clinical follow-up, genotyping, and new biomarker data.

TITLE: Cognitive Dysfunction Neuropsychiatric SLE NIAMS
P.I.: Michael D. Lockshin, M.D.
INSTITUTION: BVC-Hospital for Special Surgery, NY
GRANT NO.: 1R01AR049165-01
KEYWORDS: Systemic Lupus Erythematosus, atherosclerosis
TYPE STUDY: Clinical
AMOUNT: $100,000

Neuropsychiatric SLE consists of 19 defined neuropsychiatric syndromes, of which cognitive dysfunction is one of the most disabling and least understood. Cognitive dysfunction occurs in more than 25% of SLE patients. In some patients cognitive dysfunction is due to stroke, but in others its cause is unknown. Autoantibody-induced neuronal cytotoxicity is a possible cause for cognitive dysfunction, and autoantibody to the NMDA receptor may play a role in cognitive dysfunction. This project will characterize cognitive dysfunction in patients in whom lupus disease activity, damage, atherosclerosis, and antiphospholipid antibody are quantified; to determine the association of anti-NMIDA (glutamate) receptor and antiphospholipid antibodies to cognitive dysfunction, to test whether magnetic resonance spectroscopy detects lesions that underlie cognitive dysfunction, and to delineate the relationship of MRS abnormalities to anti-NMDA receptor antibody, lupus disease activity, atherosclerosis, and antiphospholipid antibody.

TITLE: Brain Connections NIAMS
P.I.: Michelle A. Petri, M.D.
INSTITUTION: John Hopkins University, MD
GRANT NO.: 1R01AR49125-01
KEYWORDS: Systemic Lupus Erythematosus
TYPE STUDY: Clinical
AMOUNT: $40,000

Neuropsychiatric manifestations of Systemic Lupus Erythematosus (NPSLE) are both common and an important source of morbidity. Of the case definitions for NPSLE syndromes that have recently been developed, cognitive dysfunction appears to be the most prevalent. Little is known about the influence of co-morbidities or ethnicity/race on disease outcomes or the underlying biological basis for this important NPSLE syndrome. Perhaps most importantly, no rational therapeutic approach for the treatment of SLE-related cognitive dysfunction currently exists and is unlikely to be developed without a better understanding of disease mechanisms. One hundred newly diagnosed patients with SLE from 10 sites will be studied for the development of cognitive dysfunction, determined using both repeatable computerized and traditional neuropsychological tests. We will evaluate the relationship of structural and functional brain imaging (using anatomic magnetic resonance imaging and resting FDG-PET), several relevant biomarkers (antiphospholipid antibodies, cytokines and adhesion molecules) and co-morbidities (race/ethnicity, depression, fibromyalgia and corticosteroid use) to cognitive dysfunction, and the impact of cognitive dysfunction on quality of life. Factors distinguishing transient or reversible versus irreversible cognitive dysfunction will be determined using a repeated measures analysis approach. The ability to study the relationship between changes in cognitive functioning and these other variables in a group of newly diagnosed SLE patients is crucial to the successful discovery of early pathologic changes that could be potentially amenable to disease-reversing therapies.

TITLE: Identifying Genes for Neuropsychiatric Lupus NIAMS
P.I.: Nilamadhab Mishra, M.D.
INSTITUTION: Wake Forest University, NC
GRANT NO.: 1R21AR49153-01
KEYWORDS: systemic lupus erythematosus, gene expression, cerebellum, hippocampus, immunopathology, autoantibody, autoimmune disorder, cytokine, gene expression, histopathology, messenger RNA
TYPE STUDY: Basic
AMOUNT: $20,000

In brief, this project will examine the genes responsible for neurologic disturbances in murine models of SLE by microarray analysis. Systemic lupus erythematosus (SLE) is a chronic, idiopathic autoimmune disease characterized by episodic flares and progression of disease, substantial morbidity and mortality. It is a multisystern rheumatic disease with a wide variety of associated clinical neurological and psychiatric syndromes including cognitive, behavioral, affective, and/or motor manifestations that may effect up to 75 percent of SLE patients. Both morbidity and mortality remain high because of lack of understanding of the underlying mechanisms related to abnormal central nervous system (CNS) function. Although the genes responsible for neurological disturbances in SLE is not finely dissected out, preliminary studies in mouse models of lupus suggests aberrant cytokine genes expression in hippocampus and cerebellum are responsible for the neurological deficit.

TITLE: Antibodies to NR2 in SLE NIAMS
P.I.: Betty Diamond, M.D.
INSTITUTION: Yeshiva University, NY
GRANT NO.: 1R01AR49126-01
KEYWORDS: NMDA receptor, antibody, cognition disorder, systemic lupus erythematosus, glutamate receptor, inhibitor/antagonist, clinical research, human tissue
TYPE STUDY: Clinical
AMOUNT: $40,000

Cognitive impairment occurs in a large percent of lupus patients. We have recently demonstrated that a subset of anti-DNA antibodies in patients with Systemic Lupus Erythematosus (SLE) binds to a defined linear epitope on the NR2 NMDA receptor. These antibodies can be found in the cerebrospinal fluid (CSF) as well as in serum. This project will explore further the antigenicity of the NR2 receptor in SLE and the functional consequences of anti-receptor antibodies. The serum from lupus patients will be studied to determine whether there are antibodies to other epitopes that function as a receptor agonists or antagonists and whether there is T cell recognition of NR2 epitopes. Also rodent models will be studied to determine whether serum antibody can penetrate an intact blood-brain-barrier, what concentrations of antibody that must be present in the CSF to cause disease, and whether there are selectively vulnerable populations of neurons. The overall goal of this collaborative interactive program is to develop the scientific foundation for prevention therapies for cognitive decline in SLE.

TITLE: Brain Cell Death in MRL Mice: Targets and Mechanisms NIAMS
P.I.: Boris Sakic, Ph.D.
INSTITUTION: McMaster University, Ontario Canada
GRANT NO.: 1R21AR49163-01
KEYWORDS: Systemic Lupus Erythematosus, brain cell death
TYPE STUDY: Basic
AMOUNT: $100,000

This research will elucidate pathogenic mechanisms of neuropsychiatric systemic lupus erythematosus by studying neuroimmunologic disease in autoimmune MIRL-Ipr mice. Lymphoid cell infiltration into the choroid plexus, neuronal atrophy, CSF neurotoxicity and an anxiety/depessive behavioral state in MRL-Ipr mice suggest that cytotoxic cells and metabolites in the CSF accelerate apoptosis in limbic regions, thus accounting for altered performance in tasks reflective of emotional reactivity and motivation. The project aims to examine: 1. Whether DNA fragmentation involves neurons, glial and/or endothelial cells (will be achieved by combining immunofluorescence with TUNEL staining). 2. Whether population of periventricular brain stem cells is susceptible to neurotoxic effects of CSIF (will be achieved by culturing neurospheres and assessing the effects of incubation with CSF from MRL-Ipr mice). 3. Whether brain cell death involves apoptotic pathways (will be achieved by examining nuclear morphology with electron microscopy, by detecting DNA laddering with chemilumnescent method and caspase activation with immunohistochemistry). 4.whether immunosuppression prevents neurodegeneration and CSF neurotoxocity.

TITLE: Tau Lymphocyte Dysfunction in Lupus Erythematosus NIAMS
P.I.: Gary M. Kammer, M.D.
INSTITUTION: Wake Forest University, Winston-Salem, NC
GRANT NO.: 2R01AR039501-12
KEYWORDS: systemic lupus erythematosus, autoimmune disease, protein kinase A, isozyme, heritability
TYPE STUDY: Basic
AMOUNT: $100,000

Systematic lupus erythematosus (SLE) is an autoimmune disorder of indeterminate etiology characterized by impaired T cell effector functions. The investigators have demonstrated impaired protein kinase A-catalyzed protein phosphorylation due to deficient type I protein kinase A (PKA-I) isozyme activity. Deficient isozyme activity predominantly reflects markedly reduced or absent type I regulatory beta (b) subunit protein (RIb). This research will investigate the hypothesis that deficient PKA-I isozyme activity is an integral signaling disorder that results in impaired $CD4^+$- and $CD8^+$ –mediated helper and cytotoxic functions, respectively, which can be partially reconstituted by restoring physiologic PKA-I activity. The objective is to investigate the molecular basis of how defective signaling via the PKA-I isozyme contributes to these abnormal T cell functions. The specific aims are: 1) To investigate the mechanisms regulating RIb protein and transcript turnover in T cells. 2) To determine whether deficient PKA-I activity exists in each of the principal subsets of SLE T cell for a specific SLE T cell subset. 2a) To demonstrate that deficient isozyme activity is associated with down-regulation of surface $CD59^+$ expression. 3) To examine the role of the RIb_2C_2 holoenzyme in T cell effector functions in SLE and normal T cells. 3a) To transiently transfect autologous RIb $_C$DNA into $CD4^+$ and $CD8^+$ T cells from SLE subjects to determine whether reconstitution of RIb protein and physiologic PKA-I activity restores T cell effector functions. 3b) To determine whether transient transfection of a RIa and/or RIb dominant-negative mutant impairs T cell effector functions. 4) To perform SLE multiplex family studies to determine 4a) The prevalence of RIb protein deficiency. 4b) Whether deficient PKA-I activity due to reduced/absent RIb protein is a heritable disorder in families of lupus probands. The significance of this research is its potential to explain how defective signaling circuitry within the T cell can lead to the aberrant T cell effector functions that result in lupus immunopathogenesis.

TITLE: Rheumatic Disease Sera: Probes of Disease Mechanism NIAMS
P.I.: Livia Casciola-Rosen, Ph.D.
INSTITUTION: Johns Hopkins University, Baltimore, MD
GRANT NO.: 2R01AR044684-05A1
KEYWORDS: autoimmune myositis, polymyositis, apoptosis, autoantigens, EF1-alpha, autoimmune disease
TYPE STUDY: Basic
AMOUNT: $100,000

Lack of specific therapies for systemic autoimmune rheumatic disease contributes to the high human burden from these diseases in the population. Development of effective and specific therapies requires the definition of pathways important in disease pathogenesis. Human autoantibodies from patients with these diseases constitute powerful probes of such pathways. The long-term goals of this proposal are to define the molecular mechanisms responsible for specific targeting of autoantigens in systemic autoimmune diseases, and thereby provide insights into the critical pathways of disease initiation and propagation. The majority of autoantigens targeted across the spectrum of systemic autoimmune diseases are unified by their clustering in the surface blebs of apoptotic cells, and their susceptibility to efficient cleavage by granzyme B during cytotoxic lymphocyte granule-induced apoptosis. The generation of unique fragments by granzyme B is a unique feature of autoantigens, implicating the ctotoxic lymphocyte granule pathway in the selection of molecules for a high titer autoantibody response. Since the cytotoxic lymphocyte granule pathway is widely active in vivo the absence of autoimmunity, additional undefined elements likely play critical roles in autoimmune disease pathogenesis. The pathology in systemic autoimmune diseases is characteristically patchy, with inflamed and damaged areas immediately adjacent to apparently normal tissue. The investigators have recently observed that numerous autoantigens (which are granzyme B substrates) undergo mitosis-specific phosphorylation leading to an SDS-stable conformational change. The investigators propose that cycling cells within inflamed tissue are differentially antigenic relative to the quiescent cells in the adjacent healthy tissue, and the pathogenic immune response in systemic autoimmunity is directed exclusively against the cycling subset of cells. This hypothesis will be pursued by (i) defining the unique biochemistry and cell biology of cytotoxic lymphocyte-induced cell death of cells at different stages of the cell cycle, (ii) studying cell cycle status and autoantigen fragmentation in vivo to determine whether there is evidence of preferential cytolysis of proliferating target cells in tissues from patients and animals with systemic autoimmune diseases, and (iii) defining the role of the granzyme B pathway and cell cycle status in initiation and propagation of systemic autoimmunity in vivo, using mice with defects in cell cycle regulation and the granzyme B pathway.

TITLE: TGF-beta Receptor Signaling in Scleroderma NIAMS
P.I.: Maria Trojanowska, Ph.D.
INSTITUTION: Medical University of South Carolina
GRANT NO.: 2R01AR044883-05
KEYWORDS: systemic sclerosis, scleroderma, fibrosis, CTGF, connective tissue growth factor, TGF-beta, transforming growth factor-beta, IGFBP5, insulin-like growth factor binding protein-5
TYPE STUDY: Basic
AMOUNT: $100,000

Organ fibrosis, a major pathological manifestation of scleroderma (SSc), is the result of excessive position of collagen I and other extracellular matrix (ECM) proteins. Despite the significant progress that has been made towards unraveling the physiological and pathological mechanisms involved in regulation of collagen genes, a full understanding of these processes is still lacking. In particular, very little is currently known about the molecular mechanism responsible for constitutive upregulation of ECM proteins by SSc fibroblasts. Such knowledge is critical for the development of suitable targets for therapeutic intervention. Previously, the investigators proposed to test the hypothesis that autocrine TGF-$ signaling through overexpression of TGF-$ receptors is at least partially responsible for the SSc phenotype. To test this hypothesis, they blocked GF-b signaling by overexpressing a kinase-deficient TGF-$ receptor II (I$R33)K). Contrary to expectations, SSc fibroblasts were mainly unresponsive to this treatment with regard to collagen production. However, this treatment resulted in a significant downregulation of the ECM production in healthy skin fibroblasts. These results led to a revision of their hypothesis and promoted them to investigate alternate mechanisms that may be responsible in the SSc phenotype. To investigate TGF-$ independent pathways, they have focused on CTGF (connective tissue growth factor) and IGFBP5 (IGF binding protein 5). The current research proposal is based on the novel observations indicating that CTGF induction of ECM in human fibroblasts is dependent on insulin signaling and that IGFBP5 also stimulates collagen production by fibroblasts. The following Specific Aims are proposed to test the hypothesis that interactions between TGF-$, CTGF, and insulin/IGF pathways are involved in the regulation of the SSc phenotype. In Specific Aim 1 they will continue to examine the role of the components of the TGF-$ signaling pathway in the manifestation of the SSc phenotype. In Specific Aim 2 they will determine the role of the CTGF-mediated pathway in ECM production SSc fibroblasts. The mechanism of CTGF stimulation of the COL1A2 promoter and characterize the components of the insulin/IGF signaling pathway that contribute to CTGF-$ induction of collagen. In Specific Aim 3, they will determine the mechanism of IGFBP5 stimulation of collagen production by SSc and healthy fibroblasts. They will analyze expression patterns of IGFBPs in SSc and healthy fibroblasts and utilize purified IGFBP proteins and corresponding cDNAs to probe their role in collagen regulation by SSc and healthy fibroblasts. In Specific Aim 4, they will examine the in vivo expression of the TGF-$ receptor subunits, CTGF, and IGF/IGFBPs in SSc skin.

TITLE: Autoimmunity Center of Excellence NIAID
P.I.: Leonard Chess, M.D.
INSTITUTION: Columbia University College of Physicians & Surgeons, New York, NY
GRANT NO.: 5U19AI46132-04
KEYWORDS: Multiple Sclerosis, Type 1 diabetes, scleroderma, systemic lupus erythematosus, rheumatoid arthritis
TYPE STUDY: Clinical
AMOUNT: $75,000

This Center will establish an interdisciplinary basic and clinical research program to focus on the evaluation of novel therapeutic approaches to five autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, and scleroderma. The investigators hypothesize that there are four principal events involved in the immunopathogenesis of these diseases: 1) predisposing genes establish a T-cell repertoire capable of recognizing self peptides intrinsic to the autoimmune process; 2) previously tolerant autoreactive CD4+ T-cell clones become activated and expand to change the T-cell repertoire to reflect autoreactive effector T-cells; 3) regulatory mechanisms, including the activation of TH1 and TH2 CD4+ T-cell subsets as well as those involving CD8 T-Cells fail, through processes such as clonal deletion or changes in the cytokine milieu; and 4) pathogenic autoantibodies develop through cognitive T-cell B-cell interactions which effect tissue injury. In these diseases one would predict that reducing the clonal expansion of relevant autoreactive T-cell by blockade of T-cell receptor signaling or interruption of the CD40 ligand-dependent pathway could down modulate disease activity. Also, interruption of the inflammatory effector functions of T-cell mediated by TNF or CD40L would similarly reduce disease potential. These hypotheses will be tested during the natural history of disease and during specific immune interventions.

TITLE: Virginia Mason/UCHSC Autoimmune Center NIAID
P.I.: George S. Eisenbarth, M.D.
INSTITUTION: University of Colorado, Denver, CO
GRANT NO.: 1U19AI50864-03
KEYWORDS: autoimmunity, diabetes, Rheumatoid Arthritis
TYPE STUDY: Translational
AMOUNT: $200,000

This grant consists of 3 research projects. The overall objective of this application is to derive markers of autoimmune

disease in its preclinical phases that would allow identification of individuals at high risk and the design of a rational prevention strategy. The projects deal in genetic, immunologic and environmental determinants that lead to disease. Project 1 will use tetramers to analyze the peripheral antigen-specific T cell profile in IDDM. Project 2 will identify three cohorts of individuals at increased risk for RA and
attempt to define immunologic markers for this risk and subsequently derive prevention strategies based on this information. The third project will identify three population-based cohorts at high risk for celiac disease and study these for environmental and genetic factors leading to disease.

TITLE: Autoimmunity: Treatment by Co-stimulatory Signal Blockade NIAID
P.I.: Samia J. Khoury, M.D.
INSTITUTION: Brigham and Women's Hospital, Boston, MA
GRANT NO.: 5U19AI46130-04
KEYWORDS: Multiple sclerosis, inflammatory bowel disease, psoriasis, autoimmunity
TYPE STUDY: Clinical
AMOUNT: $75,000

A Center of Excellence for Autoimmunity will be established at the Brigham and Women's Hospital. Projects supported under this initiative will focus on the study of therapy of autoimmune diseases by blocking co-stimulatory signals. Investigators will focus on the CD40-CD40L pathway. The human diseases of major focus are multiple sclerosis, inflammatory bowel disease, and psoriasis. All are organ specific diseases where T-cells appear to be essential in initiating the immune response and lead to the particular disease pathology. Four projects are supported. The overall goals of project 1 are to study in a pilot trial the efficacy and safety of anti-CD40L therapy in multiple sclerosis. The goals of project 2 are to study in a pilot trial the efficacy and safety of anti-CD40L therapy in inflammatory bowel disease. Project 3 will focus on the immunologic changes associated with anti-CD40L therapy in patients with multiple sclerosis and inflammatory bowel disease. Project 4 will study the immune mechanisms of psoriasis. Data obtained from the pilot studies will be useful in designing Phase m clinical trials, and immunologic investigations will help to identify surrogate markers for disease activity.

TITLE: Denver Autoimmunity Center of Excellence NIAID
P.I.: Brian L. Kotzin, M.D.
INSTITUTION: University of Colorado Health Sciences Center, Denver, CO
GRANT NO.: 5U19AI46374-04
KEYWORDS: Type 1 diabetes, lupus nephritis, Rheumatoid Arthritis, kidney
TYPE STUDY: Clinical and basic
AMOUNT: $75,000

A Center of Excellence for Autoimmunity will be established at the University of Colorado Health Sciences Center. The Center builds on a strong research and clinical base in Type 1 diabetes, celiac disease, systemic lupus, rheumatoid arthritis, multiple sclerosis, autoimmune skin disease, autoimmune pulmonary disease and other autoimmune disorders. Under this initiative, two clinical trials will be conducted. Clinical Project 1 will evaluate subcutaneous insulin vaccination to prevent the appearance anti-islet autoantibodies in infants at high risk for the development of autoantibodies and disease. Clinical Project 2 will test humanized anti-C5 mAbs in patients with active lupus nephritis. Three basic components will be studied: 1) to define the T-cell specificities and distribution of insulin-and islet antigen-reactive T-cells in murine models and patients with Type 1 diabetes; 2) to determine the effects of inhibition of IL-18 and complement on cytokine production and disease in collagen-induced arthritis and rheumatoid synovion; and 3) to define the non-MHC genetic contributions to different clinical subtypes of autoimmune polyendocrine syndrome II. These basic projects will provide important information to design future clinical trials, to monitor the effectiveness of immunologic therapies, and/or provide surrogate markers to correlate with immunologic therapies in autoimmune diseases.

TITLE: Penn Autoimmunity Center of Excellence NIAID
P.I.: A.M. Rostami, M.D., Ph.D.
INSTITUTION: University of Pennsylvania, Pennsylvania, PA
GRANT NO.: 5U19AI146358-04
KEYWORDS: Multiple Sclerosis, systemic lupus erythematosus, autoimmunity
TYPE STUDY: Clinical and basic
AMOUNT: $75,000

A Center of Excellence for Autoimmunity at the University of Pennsylvania School of Medicine will be established. It will consist of four projects (three clinical and one basic) and two cores. The clinical component of the Center consists of three clinical trials: 1) a Phase I/II trial on the use of antibody to Interleukin-12 for the treatment of multiple sclerosis; 2) a Phase I/II trial on the use of Interleukin-12 in the treatment of inflammatory bowel disease; and 3) the use of anti-CD20 antibody for the treatment of systemic lupus erythematosus. The basic science component is focused on the elucidation of the basic mechanisms of autoimmunity and immuno-modulation related to the clinical trials. Investigators will study the role of IL-12 in the pathogenesis and therapy of multiple sclerosis and its animal counterpart, experimental autoimmune encephalomyelitis. Also, they will focus on the mechanisms of anti-B-cell therapy in systemic lupus erythematosus and its murine model. An immunology core and an administrative core will be supported under this initiative.

TITLE: T-Cell Reconstitution After Stem Cell Autograft NIAID
P.I.: Jan Storek, M.D., Ph.D.
INSTITUTION: Fred Hutchinson Cancer Research Center, Seattle, WA
GRANT NO.: 5R01A146108-04
KEYWORDS: autoimmunity
TYPE STUDY: Clinical
AMOUNT: $60,000

The goal is to evaluate how the T cell repertoire is reestablished in patients with autoimmune diseases who have undergone lymphocytopenia from high dose chemotherapy/radiation plus anti-thymocyte globulin followed by reconstitution with autologous transplantation of hemopoietic (CD34+) precursors. The hypothesis is that in young individuals, a substantial number of regenerating T cells originate from hemopoietic progenitors whereas in older individuals, the vast majority of T cells originate from the expansion of preexisting T cells. The techniques used will be spectra typing, sequencing of the T cell receptor genes withing a single spectra typing band and quantifying T cells that contain T cell receptor-rearrangement circles.

TITLE: How Does Blockage of CD40/CD40L Prevent Autoimmunity? NIAID
P.I.: Matthias Von Herrath, M.D.
INSTITUTION: Scripps Research Institute, La Jolla, CA
GRANT NO.: 1U19AI51973-02
KEYWORDS: autoimmunity, diabetes
TYPE STUDY: Basic - Animal Models
AMOUNT: $100,000

This grant consists of two Pilot Projects, three Projects, and two Cores. Investigators will use three different models of autoimmune diseases to analyze effector functions of dendritic cells, lymphocytes, and regulatory antigen presenting cells. The Program focuses on the blockade of a single pathway and it's study in several different autoimmune scenarios. The program utilizes some novel techniques and is studying the detailed mechanism by which CD40L blockade effectively prevents the development of autoimmunity.

TITLE: Mechanism of Copaxone Therapy in Multiple Sclerosis NIAID
P.I.: Michael Racke, M.D.
INSTITUTION: UT Southwestern Medical Center at Dallas, TX
GRANT NO.: 5R01A147133-04
KEYWORDS: Multiple sclerosis, autoimmunity
TYPE STUDY: Clinical
AMOUNT: $140,000

Multiple Sclerosis (MS) patients are categorized on the basis of whether they have clearly defined relapses, relapsing-remitting MS (RRMS), or whether they are progressing. Progressing patients are further divided on the basis of whether they initially experienced relapses (secondary progressive MS), or whether they deteriorate slowly without evidence of relapses or remissions (primary progressive MS). One question is whether the patients with primary progressive MS (PPMS) differ from the patients with secondary progressive MS or whether they represent different aspects of a clinical pathologic spectrum. This group has shown that patients with RRMS have myelin-reactive T cells that are less dependent upon costimulation than myelin-reactive T cells from normal controls. The goal is to test the hypothesis that myelin-reactive T cells in patients with PPMS can be distinguished from naive myelin-reactive T cells by a lack of dependence upon costimulation for activation and that costimulatory requirements for these myelin-reactive T cells change during the course of disease. Glatiramer acetate (Cop-1, Copaxone) has previously been shown to reduce the number of relapses in RRMS and is now being tested for efficacy in patients with PPMS. It is unclear how Copaxone exerts its therapeutic effect. This study will determine whether Glatiramer alters cytokine secretions of myelin-reactive T cells and the T cell repertoire in PPMS.

TITLE: EBNA-1 in Lupus NIAID
P.I.: John B. Harley, M.D.
INSTITUTION: Oklahoma Medical Research Foundation
GRANT NO.: 2R01AI31584-09
KEYWORDS: Systemic Lupus Erythematosus, Epstein-Barr virus
TYPE STUDY: Basic
AMOUNT: $200,000

The environmental factors associated with systemic lupus erythematosus (SLE) include Epstein-Barr virus (EBV). Once infected, EBV is well known to persist in all human hosts for life. Novel approaches to the detection of this pathogen and to the assessment of the host response to this pathogen are warranted. Among the most interesting viral products is Epstein-Barr virus Nuclear Antigen-1(EBNA-1), which contains a peptide sequence that inhibits antigen presentation and class 1 HLA-dependent cytotoxic T cell responses. Preliminary data show that EBNA-1 also contains sequences that appear to be differentially bound by SLE as opposed to normal sera. SLE will be studied from the perspectives of the anti-EBNA-1 humoral immune response, of EBNA-1 expression in B cells and of EBNA-1 sequence variants.

TITLE: Sex Hormone Regulation of Innate Immunity in Women and Men NIAID
P.I.: Charles R. Wira, Ph.D.
INSTITUTION: Dartmouth Medical School, Lebanon, OH
GRANT NO.: 1P01AI051877-01
KEYWORDS: sex hormones, immune responses, Female Reproduction Tract (FRT), sexually transmitted diseases
TYPE STUDY: Basic
AMOUNT: $300,000

This program from a well established senior investigator will evaluate the hypothesis that sex hormones regulate the innate and potentially the adaptive immune responses. This project, which includes an abundance of preliminary data, utilizes cutting edge technologies to investigate the role of epithelial cells of the Female Reproductive Tract (FRT), which form the front line of defense against sexually transmitted diseases. The principle investigator previously demonstrated that sex hormones influence antigen presentation and immunoglobulin levels in uterine secretions. A unique approach with exceptionally strong initial data to investigate the effects of estradiol on NK (Natural Killer) cells in the FRT is incorporated. The two other projects are more preliminary and descriptive. These projects will study the effect of sex hormones on the function of polymorphonuclear neutrophils and the maturation of dendritic cells in the FRT. Since little is known about the effects of hormones on these cells in the FRT, this is the state of the science. This synergetic program will lead to a greater understanding of the mechanisms by which sex hormones affect the innate immune system and the response to pathogens. Novel approaches to prevention of infectious diseases of the FRT could be developed with increased knowledge. This research will also be supported by Office of AIDS Research.

TITLE: Investigating IL-6 Experimental Myasthenia Gravis NIAID
P.I.: Premkumar Christadoss, M.D.
INSTITUTION: University of Texas Medical Branch, Galveston, Texas
GRANT NO.: 1R01AI049995-01A1
KEYWORDS: autoimmune myasthenia gravis (EAMG), acetylcholine receptor (AChR), immunotheraphy
TYPE STUDY: Basic
AMOUNT: $294,570

Studies suggest a pivotal role for IL-6, TNF, and IL-18 in development of experimental autoimmune myasthenia gravis (EAMG), because a dramatic suppression of clinical EAMG was observed in IL-6, TNF receptor p55 p75, or IL-18 gene KO mice in the B6 background. The precise cellular and molecular mechanisms by which IL-6, TNF, and IL-18 contribute to EAMG pathogenesis are not known. The central hypothesis is that IL-6 contributes to EAMG pathogenesis by activating acetylcholine receptor (AChR)-specific T and B cells and germinal center (GC) formation, promoting secondary anti-AChR IgG antibodies and activation of the C3 component of complement. The immunopathological and clinical effects will be evaluated by in-vivo IL-6 administration in B6 and IL-6 KO mice during primary and/or secondary immunizations with AChR. Clinical and immunopathological signs of EAMG will be induced in B6 mice by in vivo administration of IL-6 after priming with AChR. AChR-primed LNC will be exposed to IL-6 and its effect on anti-AChR IgM and IgG isotopes will be evaluated. Also, we will examine whether IL-6 and TNF act in concert or regulate one another in mediating EAMG. B7-1 gene-deficient or B7-1 molecule-blocked mice, and B6 mice will be immunized with AChR, and the effect evaluated of B7-1 deficiency for blocking in EAMG development and production of II-6 and TNF. To prevent EAMG, antibody to IL-6 will be administered with primary and/or secondary immunizations with AChR. To ameliorate established clinical EAMG, antibody to IL-6 will be administered after clinical signs are established. Finally, combination of immunotheraphy will be performed with high-dose AChR T cell epitope tolerance and IL-6 neutralization in B6 mice. If IL-6 is involved in activating pathogenic AChR-specific B cells, forming GC, and upregulating and activating C3 and if in vivo blocking of IL-6 function induces remission of established clinical EAMG, then IL-6 antagonist could be used in MG therapy. To avoid non-specific immunosuppression by IL-6 antagonists, high-dose AChR T cell epitope tolerance could be given as maintenance therapy after the first course of combination immunotheraphy.

TITLE: Mechanisms of T-cell Induced-APC Cytotoxicity in Lupus NIAMS
P.I.: Mariana J. Kaplan, M.D.
INSTITUTION: University of Michigan, Ann Arbor, MI
GRANT NO.: 1K08AR048235-01
KEYWORDS: systemic lupus erythematosus, autoimmune disease, apoptosis, autoantigens
TYPE STUDY: Basic
AMOUNT: $100,000

The application proposes funding with the specific intent of developing an independent research program by the principal investigator. The applicant has been pursuing basic science research in the areas of T cell immunology and pathogenesis of lupus (SLE) for the past four years. The proposal is a natural extension of the applicant's current research on monocyte/macrophage (Mø) apoptosis. Apoptosis-inducing molecules mediate the autologous monocyte/Mø killing caused by $CD4^+$ lupus T cells. Target cell killing by this mechanism can lead to the generation of autoantibodies. The specific aim is to determine the pathways involved in monocyte/Mø apoptosis induced by lupus $CD4^+$ T cells. The applicant will test whether it is possible to inhibit the development of autoimmunity in an SLE animal model, by blocking the apoptotic pathways involved in monocyte/Mø killing by autoreactive $CD4^+$ T cells. The role of the macrophage apoptosis in triggering or augmenting autoimmunity will also be investigated. Methods: a) Measurement of cell surface expression of

death-receptor ligands on SLE and control T cells by flow cytometry. b) With cytotoxicity assays, determine whether these apoptotic pathways are functional in SLE moncyte/Mø and whether blocking these can inhibit the autologous moncyte/Mø killing by SLE T cells. c) Given the redundancy of the pathways involved in Mø cytotoxicity, the applicant will test, in vitro, if inhibiting the death signals downstream of the death receptors (FADD, caspases, FLIP) is sufficient to inhibit monocyte/Mø apoptosis induced by these ligands. d) In vivo studies will try to characterize whether the blockade on monocyte/macrophage death-receptor ligands by monoclonal antibodies or fusion proteins, can inhibit the development of murine SLE, and whether the elimination of tissue macrophages per se (with clodronate liposomes in vivo) is sufficient to induce autoimmunity in an animal model. The results of the studies proposed might identify potential mechanisms involved in the generation of autoantigens in SLE. These could lead to the development of novel therapeutic interventions designed to reverse these abnormalities and abrogate or block the onset and severity of this disease. The sponsor and the institution are committed to contributing protected time, career development and resources to the applicant.

TITLE: Studies of Collagen Gene Regulation in Two Murine Models NIAMS
P.I.: Stephen H. Clark, Ph.D.
INSTITUTION: University of Connecticut, Farmington, CT
GRANT NO.: 1R01AR48082-02
KEYWORDS: Scleroderma, fibroblasts, microarrays, autoimmunity
TYPE STUDY: Basic - Animal Models
AMOUNT: $200,000

This research project will utilize two mouse mutations that are models for Scleroderma, tight skin (Tsk) and tight skin2(Tsk2). Both mutations display excessive accumulation of collagen and other extracellular matrix components in the skin, a hallmark of the human disease. The long-range objective of this research is to utilize the two mutations, combined with several lines of transgenic mice as experimental tools, to dissect molecular mechanisms of disease pathogenesis.

TITLE: Fine Specificity of Scleroderma Autoantibodies NIAMS
P.I.: Judith James, M.D.
INSTITUTION: Oklahoma Medical Research Foundation, Oklahoma, OK
GRANT NO.: 1R01AR48045-02
KEYWORDS: Scleroderma, immune response, clinical research, autoimmunity
TYPE STUDY: Translational
AMOUNT: $200,000

This application addresses the important problem of the significance of autoantibodies in Scleroderma patients. The project proposes to identify the initial epitope on nRNP and topoisomerase I which is identified by sera from patients with Scleroderma. This will lead to the search for a pathogen in the environment which could lead to an immune response to the cross-reacting antigen. The possibility of tissue damage due to autoantibodies will also be investigated.

TITLE: Registry and Repository of African Americans with Rheumatoid Arthritis NIAMS
P.I.: Larry Moreland, M.D.
INSTITUTION: University of Alabama at Birmingham, Birmingham, AL
GRANT NO.: 1N01AR002247-000
KEYWORDS: African American, Rheumatoid Arthritis, autoimmunity
TYPE STUDY: Clinical
AMOUNT: $200,000

This 5-year project will be housed at the University of Alabama at Birmingham. It will establish a Consortium for the Longitudinal Evaluation of African Americans with Early Rheumatoid Arthritis registry which serves to identify genetic and non-genetic prognostic factors of disease outcome using radiographic presence of bony erosions as the primary outcome measure (at 3 years disease duration). The registry will serve as the basis for prospective analyses of factors predictive of the clinical phenotype and outcomes. Four major academic medical centers in the southeast U.S. will gather data which will provide a resource for investigators interested in the genetics of RA in AA. The CLEAR registry will be utilized to examine the hypothesis that HLA-DR alleles and cytokine polymorphism in the tumor necrosis factor- alpha [TNF-alpha]/lymphotoxin (LT)- alpha, interleukin-1 (IL-1), and IL-6 loci, predict the presence or absence of erosion on hand and feet radiographs at 3 years disease duration in AA. The principal investigator, Dr. Larry Moreland, is a clinical researcher whose primary research interest has been the evaluation of biologic response modifiers (and their mechanisms) which are targeted at the disease process in rheumatoid arthritis.

INFECTIOUS DISEASES

TITLE: Sex in Viral Myocarditis NIAID
P.I.: Sally A. Huber, Ph.D.
INSTITUTION: University of Vermont
GRANT NO.: 1 R21 AI51850-01
KEYWORDS: autoimmunity, myocarditis, hormones, host defense responses
TYPE STUDY: Translational

AMOUNT: $50,000
Myocarditis is an inflammatory disease of the myocardium. Approximately 65% of cases follow recent enterovirus infections and occur in males. As in humans, CVB3 infections cause severe myocarditis in male, but not virgin female mice. Androgens (progesterone and testosterone) increase virus receptor expression on cardiac myocytes while 17-beta-estradiol treatment does not. Since lymphocytes also express CVB3 receptors, we hypothesize that hormones might modulate lymphocyte expression of these molecules as well. Cytokine release differs between male and female lymphocytes with male cells producing interferon (IFN)gamma and female cells producing interleukin (IL)-10. We hypothesize that viruses, which have repetitive symmetry of the virus capsid, cross-link important cell surface molecules on lymphocytes and cause rapid non-antigen-specific lymphocyte activation. These studies may provide new insights as to how viruses affect developing host defense responses and how hormones can modulate this initial response.

TITLE: Mid-America Adolescent STD Cooperative Research Center NIAID
P.I.: Donald Orr, M.D.
INSTITUTION: Riley Hospital, Indianapolis, IN
GRANT NO.: 5U19AI43924-05
KEYWORDS: Infectious diseases, sexually transmitted diseases, prevention, behavior
TYPE STUDY: Clinical
AMOUNT: $50,000
Sexually transmitted diseases (STD) produce very serious outcomes in women, regardless of race, and often affect their infants as well. In addressing the racial health disparities in the occurrence of STD, NIAID supports Sexually Transmitted Diseases Cooperative Research Centers (STDCRCs), which provide a multi-disciplinary approach to research in the area of STD by bringing together basic science, clinical and epidemiological research, and behavioral intervention strategies for the prevention and control of STD.

MENOPAUSE

TITLE: Study of Women's Health Across Nation II: (SWAN II) NIA
P.I.: Dr. Mathews, Coordinating Center, Multiple sites and investigators plus a lab
INSTITUTIONS: New England Research Institute, Watertown, MA
GRANT NO.: 5U01AG12546-09
KEYWORDS: Menopause, aging, hormones, minorities, risk factors, disease
TYPE STUDY: Clinical
AMOUNT: $250,000
SWAN consists of both cross sectional and longitudinal studies on the natural history of menopause and a characterization of endocrinology/physiology of premenopause. Five ethnic groups are included - Caucasian, African American, Hispanic, Chinese, and Japanese. There are 7 sites across the country - Boston, Pittsburgh, Chicago, Michigan, UCLA, UC Davis and New Jersey. For the cross-sectional study, there are approximately 16,000 women enrolled ranging in age from 40-55 years to determine the age of menopause. The longitudinal study has approximately 3150 women (450 at each site) between the ages of 42-52 to determine menopause-specific physiological changes and their predictors and the impact of menopause on subsequent disease. Measurements are being made of the major reproductive axis hormones (LH, FSH, estradiol, progesterone, and testosterone), adrenal markers of aging (DHEAs), other endocrine markers (TSH, sex hormone binding globulin [SHBG]) and new ovarian markers which have the potential to define the menopausal transition and the postmenopause.

TITLE: Centers for Dietary Supplements Research: Botanicals NCCAM
P.I.: Norman Farnsworth, Ph.D.
INSTITUTION: University of Illinois at Chicago, IL
GRANT NO.: 5P50AT00155-04
KEYWORDS: Botanicals, menopause, black cohosh, red clover, CAM
TYPE STUDY: Clinical and basic
AMOUNT: $100,000
This multi-disciplinary team of investigators will focus on the study of the safety and efficacy of botanicals used to treat women for menopause. Studies will address mechanisms of action, identification of active compounds, and characterization of metabolism, bioavailability and pharmacokinetics of active species in these botanicals. The research component will consist of the following: 1) A pharmacognosy project to carry out standardization of botanical dietary supplements and structure elucidation of active compounds; 2) Isolate active compounds for structure elucidation, and then to determine the mechanism(s) of action of botanicals; 3) Study the metabolism, absorption and toxicity of active compounds in botanicals including immunotoxicity; and 4) Carry out phase I and II clinical trials of black cohosh (*Cimicifugai racemosa)* and red clover (*Trifolium pratense*).

TITLE: Menopausal Depression: Chronobiologic Basis NIMH
P.I.: Barbara L. Parry, M.D.
INSTITUTION: University of California, San Diego, La Jolla, CA
GRANT NO.: 5R01MH059919-03
KEYWORDS: depression, menopause, hormone replacement therapy, behavior
TYPE STUDY: Clinical
AMOUNT: $100,000

The specific focus of this project will be to examine the effects of estradiol and progesterone administration on circadian rhythms in humans. The subjects will be healthy postmenopausal women. The investigators will test the hypothesis that estrogen advances the phase and enhances the amplitude and synchrony (the stability of timing relationships) of biological rhythms as measured by melatonin, sleep and activity, whereas progesterone antagonizes these effects. This proposal represents an extension of the investigators' previous work that examined the effects of endogenous changes in estradiol and progesterone during the menstrual cycle on measures of mood and circadian rhythmicity. This work led to the development of new hypotheses and treatment strategies. The current proposal will allow investigation of these hypotheses further but in a more controlled design. The investigators anticipate gaining important information on possible mechanisms mediating the effects of reproductive hormones on mood and behavior and deriving relevant clinical treatment guidelines for menopausal women.

MENTAL HEALTH

TITLE: Improving Antidepressant Adherence in Older Adults NIMH
P.I.: Joanne Sirey, Ph.D.
INSTITUTION: New York Presbyterian Hospital - Cornell University
GRANT NO.: 1K23MH066381-01
KEYWORDS: antidepressant treatment, behavioral change, late-life depression, SSRI antidepressant therapy, Primary Care Physicians
TYPE STUDY: Clinical
AMOUNT: $100,000

The goal of the research within this Research Scientist Award is to provide further interdisciplinary training and research opportunities to transition the applicant to become an independent investigator in interventions research. The career goal of the applicant is to develop interventions to improve adherence to antidepressant treatment among depressed older adults in primary care. The career development objectives of this application are to learn: 1) the theories underlying behavioral change interventions; 2) the design and evaluation of interventions in late-life depression; 3) assessment of older adults' attitudes and beliefs; and 4) factors that affect treatment adherence across illness. This training will provide the knowledge and skills to assess and to address negative attitudes and beliefs about: 1) depression and the usefulness of treatment efficacy, 2) stigma, and 3) treatment self-efficacy. The research proposed will pilot the usefulness of a brief, individualized intervention to improve adherence to SSRI antidepressant therapy by older adults prescribed by Primary Care Physicians. The intervention is designed to improve adherence by addressing the negative attitudes and beliefs that are obstacles to adherence for adults with late-life depression. Although the intervention is not a therapy to reduce depression; but because depression itself can contribute to negative attitudes and beliefs, one of the goals of the intervention is to buffer the effect of depression on adherence. The intervention targets obstacles to adherence and if proven useful, would be a manualized and feasible way to reduce the personal and public health costs of undertreatment of late-life depression in older adults seen in primary care.

TITLE: Effects on Children of Treating Maternal Depression NIMH
P.I.: Anne Riley, Ph.D.
INSTITUTION: Johns Hopkins University, Baltimore, MD
GRANT NO.: 5R01MH058384-05
KEYWORDS: Mental health, maternal depression, children, environment, behavior
TYPE STUDY: Clinical
AMOUNT: $50,000

Maternal depression has devastating effects on the mental and physical health of children. This project will study the influence of treating maternal depression on children ages 5-11. This project will study 150 elementary-school aged children whose mothers are depressed (50 Hispanic, 50 African American and 50 Caucasian) and 50 comparable children whose mothers are not depressed. Their mental health and functioning will be assessed by natural raters in their environments over a two-year time period that will link child functioning, symptomatology, and psychiatric disorders to mothers' symptomatology, parenting behavior, and family environment.

TITLE: Sex Differences in Self-Evaluation: Social Factors NIMH
P.I.: Eva Pomerantz, Ph.D.
INSTITUTION: University of Illinois, Champaign, IL
GRANT NO.: 5R01MH057505-04
KEYWORDS: Gender socialization, self-evaluation, depression, mental health, behavior
TYPE STUDY: Clinical
AMOUNT: $47,599

Girls are more likely than boys to possess self-evaluative mechanisms that may heighten vulnerability to depressive and anxiety symptoms. It is hypothesized that culturally held gender stereotypes may cause parents to be more controlling in certain behavioral domains with girls than with boys. This pattern of gender socialization is expected to lead girls to be more likely than boys to possess self-evaluative mechanisms that heighten vulnerability to depressive and anxiety symptoms.

TITLE: Health Survey of Two-Spirited Native Americans NIMH
P.I.: Karina L. Walters, Ph.D.
INSTITUTION: University of Washington, Seattle, WA
GRANT NO.: 1R01MH65871-01
KEYWORDS: mental health, cultural and spiritual coping, HIV risk behaviors, Native American, alcoholism/ alcohol abuse, clinical research, human subjects
TYPE STUDY: Clinical
AMOUNT: $175,000

American Indian and Alaskan Native lesbian, gay, bisexual, transgendered, and two-spirited individuals (two spirits) are a drastically understudied and underserved group, at risk for multiple health and mental health problems. There are no national, quantitative, representative studies of this population on any topic. Building upon solid preliminary data, we will conduct structured survey interviews with 400 two spirits drawn from six sites across the U.S. With these interview data, we will test a theoretical model of stress and coping specific to this population. Sub-aims are to (a) establish preliminary prevalence rates of trauma and health outcomes (i.e., HIV sexual risk behaviors, alcohol and other drug use, and mental health indicators); (b) test the direct associations between trauma and health outcomes; (c) determine how cultural and spiritual coping factors moderate the effect of trauma on health outcomes; and (d) examine the mediating role of substance use on the trauma-HIV sexual risk behavior and trauma-mental health relationships. The results will contribute toward the refinement of a sample strategy useful in studying other hidden and stigmatized populations. Through the course of this project, we aim to develop the research infrastructure at the six community agencies comprising our participant recruitment sites in order to facilitate future goals of designing and evaluating interventions to address the urgent needs of two spirits.

MUSCULOSKELETAL SYSTEMS

TITLE: Osteo-Arthritis Initiative NIAMS
TYPE STUDY: Public-Private Partnership
AMOUNT: $800,000

The OAI is a public-private partnership that will bring together new resources and commitment to help find biological markers for the progression of osteoarthritis, a degenerative joint disease that is a major cause of disability in people 65 and older. Over 5-7 years, the Osteoarthritis Initiative (OAI) will collect information and define disease standards on 5,000 people at high risk of having osteoarthritis and at high risk of progressing to severe osteoarthritis during the course of the study. Currently, new drug development for OA is hindered by the lack of objective and measurable standards for disease progression by which new drugs can be evaluated.

The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical companies: GlaxoSmithKline, Merck, Novartis Pharmaceuticals Corporation, and Pfizer. The consortium is being facilitated by the Foundation for the National Institutes of Health, Inc. The OAI will provide approximately $8 million yearly for as many as six clinical research centers to establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data and radiological images, and a biospecimen repository. All data and images collected will be available to researchers worldwide to help quicken the pace of scientific studies and biomarker identification.

TITLE: New Methods for Monitoring Treatment for Osteoporosis NIAMS
P.I.: Richard Brand, Ph.D.
INSTITUTION: University of California, San Francisco, CA
GRANT NO.: 1R01AR048527-01A1
KEYWORDS: osteoporosis, bone mineral density (BMD), alendronate, Fracture Intervention (FIT), Multiple Outcomes of Raloxifene Evaluation (MORE)
TYPE STUDY: Clinical
AMOUNT: $100,000

The overall goal of this project is to develop improved monitoring methods for evaluating the success of a treatment on an individual patient basis using patient-specific estimates of the probability of non-response to treatment, or its complement,

the probability of response to treatment. This will provide an empirically grounded and conceptually sound statistical tool for monitoring success of treatment for osteoporosis. This project will extend recently published work in this area, which was focused on the use of a patient's pre to post treatment change in total hip bone mineral density (BMD) for judging whether or not the patient has responded to treatment with alendronate. The procedure was calibrated with data from the Fracture Intervention Trial (FIT), a randomized placebo-controlled trial, which evaluated alendronate for treatment of osteoporosis. Clinicians may be overly ready to conclude that treatment with alendronate has failed. For example, when a treated subject has no increase in total hip BMD from baseline, there is only a small probability that a treated patient has actually failed to respond to treatment. Although different from current clinical opinion, this conclusion results from proper consideration of background changes in placebo-treated control subjects as a backdrop for judging the changes in treated subjects. To make this methodology more versatile, extensions to accomplish two important goals will be developed. The first is to handle many different configurations of patient monitoring data that are typically encountered in clinical practice; e.g. repeated BMD measurements, BMD measurements at multiple sites, etc. The second is to use patient-specific characteristics such as age, race, BMI, and baseline BMD in the calculation of probability of non-response. Application of the methods to FIT data and the Multiple Outcomes of Raloxifene Evaluation (MORE) data will provide new substantive results that will 1) contribute to useful clinical guidelines for judging how well a patient is responding to osteoporosis treatment and 2) provide guidance about cost-efficient patient-monitoring strategy.

TITLE: Glucocorticoids Alter the Birth and Death of Osteoblasts — **NIAMS**
P.I.: Robert Weinstein, Ph.D.
INSTITUTION: University of Arkansas for Medical Sciences, Little Rock, AR
GRANT NO.: 5R01AR 46191-04
KEYWORDS: Glucocorticoids, osteoblasts, parathyroid hormone, osteoporosis
TYPE STUDY: Clinical and basic
AMOUNT: $100,000

This study will characterize the effects of chronic glucocorticoid excess on several aspects of bone physiology. Patients with glucocorticoid-induced bone loss will be included. The effect of alendronate (Fosamax) and parathyroid hormone will be tested in mice for efficacy in ameliorating the effect of glucocorticoids.

TITLE: Low-Dose Doxycline Effects on Osteopenic Bone Loss — **NIDCR**
P.I.: Jeffrey B. Payne, DDS
INSTITUTION: University of Nebraska, Lincoln, NE
GRANT NO.: 1R01DE12872-02
KEYWORDS: clinical trials, periodontitis, osteoporosis
TYPE STUDY: Translational, Clinical
AMOUNT: $308,924

This study seeks to demonstrate the clinical efficacy of low dose doxycycline (LDD) therapy in reducing bone loss due to periodontitis and estrogen deficiency in a postmenopausal estrogen deficient osteopenic population. Success in reducing or arresting bone loss related to periodontitis in an estrogen deficient osteopenic group would represent important progress in understanding and managing the pathophysiologic mechanisms that are involved in bone loss with this process.

NEUROLOGY

TITLE: Estrogen Induced Hippocampal Seizure Susceptibility — **NINDS**
P.I.: Catherine Woolley, Ph.D.
INSTITUTION: Northwestern University, Evanston, IL
GRANT NO.: 5R29NS037324-05
KEYWORDS: Epilepsy, hippocampus, estradiol, neurosciences research
TYPE STUDY: Basic
AMOUNT: $35,000

A significant proportion of women with epilepsy experience increased seizure frequency during phases of the menstrual cycle in which estradiol levels are elevated. This is termed catamenial epilepsy. Animal models of epilepsy also demonstrate that estradiol increases seizure susceptibility. Previous work in the adult female rat has shown that estradiol induces new dendritic spines and axospinous synapses on CA1 pyramidal cells in the hippocampus, a key brain structure in the generation and propagation of seizure activity. Furthermore, estradiol-induced dendritic spines and synapses are correlated with increased excitability of hippocampal neurons and decreased hippocampal seizure threshold. This correlation suggests that estradiol-induced seizure susceptibility in women with catamenial epilepsy may be due, at least in part, to hormone-mediated alterations in hippocampal synaptic connectivity. The studies in this proposal will use the adult female rat to test the hypothesis that estradiol facilitates seizure activity through alteration of hippocampal synaptic structure and physiology.

NUTRITION

TITLE: Food Choline Database Project — NHLBI
P.I.: John H. Himes, Ph.D.
INSTITUTION: University of Minnesota Twin Cities, Minneapolis, MN
GRANT NO.: 5U24HL61778-04
KEYWORDS: nutrition, nutrient analysis database, choline metabolism
TYPE STUDY: applied - National database
AMOUNT: $50,000

The purpose of this program is to develop a comprehensive and high-quality database on the choline content of foods commonly eaten in the United States. The data will be generated by analyzing nationally representative samples of 400 foods for their content of various forms of choline. Research activities will be managed by the US Department of Agriculture as a dovetailed component of the ongoing National Food and Nutrient Analysis Program, which has already collected the needed food samples. The total direct cost for developing the database is estimated at $400,000 (400 foods at $1000/food). The food choline database - resulting from this project will rectify serious gaps in the general knowledge of choline metabolism and requirements, which require calculating individual and population level estimates of choline intake.

TITLE: Altered Calcium and Vitamin D Metabolism in PMDD — NIDDK
P.I.: Susan Thys-Jacobs, M.D.
INSTITUTION: St. Luke's-Roosevelt Hospital Center, New York, NY
GRANT NO.: 1R01DK57869-03
KEYWORDS: PMDD, nutrition
TYPE STUDY: Clinical
AMOUNT: $100,000

Premenstrual Dysphoric Disorder (PMDD) is widely recognized as a recurrent disorder related to hormone variations of the menstrual cycle. Whereas alterations in calcium homeostasis have long been associated with many affective disturbances, recent evidence has suggested that luteal phase symptomatology may be associated with a perturbation in calcium homeostasis. The purpose of this investigation is to understand more completely the extent to which calcium regulation is disturbed in PMDD by utilizing new tools to access calcium and bone turnover. The long term objective is to elucidate the pathophysiology of PMDD as it relates to the calciotropic hormones and bone markers. The experimental design involves enrolling 70 with PMDD and 35 controls. Following two months of baseline symptom documentation, women with PMDD and controls with be enrolled in a nine month observational period with frequent hormonal samplings, urinary collections and daily ratings. Understanding the pathophysiology associated with PMDD may lead to effective therapeutic strategies to prevent the neuropsychiatric disturbances and abnormal calcium regulation that are characteristic of this disorder.

OBESITY/OVERWEIGHT

TITLE: Increasing Physical Activity Levels in Low-Income Women — NIDDK
P.I.: Barbara J. Speck, Ph.D., RN
INSTITUTION: University of Louisville, KY
GRANT NO.: 1R01DK63523-01
KEYWORDS: underrepresented minorities, physical activity, intervention
TYPE STUDY: Clinical
AMOUNT: $178,750

This project is aimed at reducing community environmental barriers to physical activity in medically underserved women. The setting for the study is a church-sponsored community center with a nurse-managed clinic that is located in a low-income neighborhood. Pretest data will include psychosocial questionnaire, physiologic (cholesterol, blood pressure), and anthropometric measures. The 6-month intervention will be two-fold: 1) provide culturally appropriate educational activities to increase women's comfort level at the community center, and 2) provide multiple culturally appropriate physical activity opportunities utilizing the gymnasium and exercise equipment. The long-term goal to establish physical activity opportunities for women at this community center that could be adapted at other community center.

TITLE: Look AHEAD (Action For Health in Diabetes) — NIDDK
INSTITUTION: Wake Forest University (coordinating center), Winston Salem, NC
Johns Hopkins University, Baylor College of Medicine, University of Colorado Health,
University of Washington, University of Tennessee, St. Lukes-Roosevelt Institute,
University of Alabama at Birmington, The Miriam Hospital, Pennington Biomedical Research,
University of Texas Health Science, University of Minnesota, University of Pittsburgh,
Massachusetts General Hospital, University of California Los Angeles, University of Pennsylvania,
Southwest American Indian Center (12 clinical centers)
KEYWORDS: Type 2 diabetes, obesity, cardiovascular, cerebrovascular,
neurosciences research, behavior

TYPE STUDY: Clinical
AMOUNT: $100,000

Is a multicenter randomized clinical trial to examine the effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term through decreased caloric intake and exercise. The Look AHEAD trial will enroll 5,000 obese patients with type 2 diabetes over a 2.5 year period. Participants will be randomly assigned to one of two interventions, the Lifestyle Intervention or Diabetes Support and Education, and will be followed for a total period of up to 11.5 years. The primary aim of Look AHEAD is to study the effects of the two interventions on major cardiovascular events: heart attack, stroke and cardiovascular death. Look AHEAD also will investigate the impact of the interventions on other cardiovascular disease-related outcomes, cardiovascular risk factors, and all-cause mortality. Additional outcomes include: diabetes control and complications, fitness, general health, health-related quality of life and psychological outcomes. The cost and cost effectiveness of the Lifestyle Intervention relative to Diabetes Support and Education will be assessed.

TITLE: Clinical and Experimental Study of Human Obesity NIDDK
P.I.: Albert Stunkard, M.D.
INSTITUTION: University of Pennsylvania, Philadelphia, PA
GRANT NO.: 5R01DK56251-06
KEYWORDS: Eating disorders, obesity, mental health
TYPE STUDY: Clinical
AMOUNT: $100,000

This project is a longitudinal study of 78 children, from 3-5 years of age, from either obese or non-obese mothers. The goal is to examine a group of variables related to food intake and energy expenditure along with measures of body size or composition, utilizing not only weight and length but measures of skinfold thickness and percent fat by dual energy x-ray absorptiometry and body water, and isotope dilution measures. The study has already found that the two independent measures of energy intake at three months of age predict body size and composition at one year of age and discounted the belief that a low total energy expenditure and maternal obesity predict body size and composition at one year of age. This study will continue to search for risk factors for obesity in the early childhood years.

PAIN

TITLE: Low Back Pain - A Multi-Center Randomized Trial NIAMS
P.I.: James Weinstein, DO
INSTITUTION: Dartmouth Medical School, Hanover, NH
GRANT NO.: 5U01AR045444-04
KEYWORDS: Neurosciences research, back pain
TYPE STUDY: Clinical
AMOUNT: $100,000

Low back pain is considered one of the most widely experienced health problems. Rates of spinal surgery have increased sharply over time and 15-fold geographic variation in rates of these surgeries has been documented. There is little evidence proving the effectiveness/efficacy of these surgical therapies over non-operative management. This study will use the resource of the National Spine Network to conduct multi-centered, randomized, controlled trials for three common diagnostic groups - lumbar intervertebral disc herniation (IDH), spinal stenosis (SpS) and spinal stenosis secondary to degenerative spondylolithesis (DS). The trials will compare the most commonly used standard surgical treatments to the most commonly used standard non-operative treatments. The primary endpoints will be changes in general health-related quality of life as measured by the SF-36 health status questionnaire and spine-related disability as measured by the Oswestry Low Back Pain questionnaire. Secondary endpoints will include patient satisfaction with treatment, resource utilization of estimation of cost, and utility for current health for estimation of quality adjusted life years.

TITLE: Sex Differences in Opioid Analgesia NIDA
P.I.: Anne Z. Murphy, Ph.D.
INSTITUTION: University of Maryland School of Medicine, Baltimore, MD
GRANT NO.: 1R01DA016272-01
KEYWORDS: opioids, gender, pain, analgesia
TYPE STUDY: Basic
AMOUNT: $293,764

Chronic pain afflicts millions of people each year. Opioid-based narcotics are the most prevalent therapeutic treatment for chronic pain management, with morphine being the most commonly prescribed. There are now well-established sex differences in the ability of morphine to alleviate pain; in animal models of acute pain, the effective dose of morphine is approximately 5-10x greater for females in comparison to males. Similar results have been reported in humans. To date, the underlying mechanisms mediating sex differences in opiate sensitivity are not known. The midbrain periaqueductal (PAG) and its descending projections to the nucleus raphe magnus (NRM) are an essential endogenous neural circuit for opioid-based analgesia. The major hypothesis is that the opiate-sensitive intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and is the major determinant of sex-based differences in opioid analgesia. Previous studies examining the dimorphic effect of opioid administration utilized acute assays of nociception. Studies proposed in Aim 1 will characterize the sexually dimorphic effect of central morphine administration using a model of chronic inflammatory pain. Preliminary data indicate that the PAG-NRM pathway is sexually dimorphic. Studies proposed in Aim 2 will use neural tract

tracing techniques to delineate the anatomical organization of the PAG-NRM spinal cord circuit in males and females. Aim 3 will examine the functional organization of this circuit in a model of prolonged inflammatory pain. The PAG is enriched in opioid receptors. Studies proposed in Aim 4 will characterize both the distribution and expression pattern of the opioid receptors. The influence of chronic inflammatory pain and gonadal steroid manipulations will also be examined. These studies will establish that the intrinsic and extrinsic circuitry of the PAG is sexually dimorphic and provide the neural substrate for sex based differences in opioid analgesia.

TITLE: Trigeminal Pain Mechanisms and Control — NIDCR
P.I.: Jon D. Levine, Ph.D.
INSTITUTION: University of California at San Francisco, San Francisco, CA
GRANT NO.: 5P01DE08973-12
KEYWORDS: pain control mechanism, orofacial neuropathies, neurosciences research
TYPE STUDY: Basic
AMOUNT: $155,237

The chemotherapeutic agent paclitaxel(Taxol) is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by parenthesis, myalgia and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine. Therefore, amelioration of the neuropathic pain might not only reduce the suffering of patients who receive paclitaxel or vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel-induced painful peripheral neuropathy in the rat. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies.

TITLE: Pain Management in Temporomandibular Joint Disorders — NIDCR
P.I.: Jennifer Haythornthwaite, Ph.D.
INSTITUTION: Johns Hopkins University, Baltimore, MD
GRANT NO.: 1R01DE13906-02
KEYWORDS: TMD, pain control, behavioral interventions, neurosciences research
TYPE STUDY: Behavioral
AMOUNT: $312,514

The primary goal of the proposed project is to test the efficacy of psychological interventions, a pharmacological intervention, and the combination of these interventions in reducing pain and improving function in persons with temporomandibular disorders (TMD). Since psychological interventions are costly and require expertise that is frequently unavailable in primary care settings, the proposed project will also examine the efficacy of a minimal contact/self help psychological intervention based on cognitive-behavioral therapy for pain management. In addition to examining the separate and combined effects of psychological and pharmacological interventions for TMD pain, the proposed study will examine whether the minimal contact cognitive-behavioral intervention can accomplish comparable reductions in pain and improvements in function relative to the therapist-administered treatment.

TITLE: Research Registries and Repository for the Evaluation of Temporomandibular Joint Implants (TMJ Device Registry) — NIDCR
P.I.: James R. Fricton, DDS, MS
INSTITUTION: University of Minnesota
GRANT NO.: N01DE22635
KEYWORDS: TMJ, medical devices
TYPE STUDY: Registry
AMOUNT: $100,000

The development of the National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository (NIDCR's TIRR) at the University of Minnesota will allow collection of clinical information and biological specimens on patients with TMJ implants throughout the United States. This will stimulate both basic and clinical studies and improve our understanding of the pathobiology of TMJ diseases and disorders. In addition, the availability of retrieved implant materials will help in the design and development of a new generation of implantable materials and advance our understanding and success of treatment of patients with TMJ implants.

PHYSICAL ACTIVITY

TITLE: Physical Activity in Older Rural midwestern Women — NINR
P.I.: Donna J. Plonczynski, MSN
INSTITUTION: University of Illinois Chicago
GRANT NO.: 1F31NR008070-01
KEYWORDS: physical activity behavior, cardiovascular risks, motivation, Model of Physical Activity Behavior (MPAB), BMI
TYPE STUDY: Clinical

AMOUNT: $26,188

The purpose of this cross-sectional study is to describe the physical activity behavior (household, work/volunteer, leisure) determinants of physical activity, and cardiovascular risks (BMI and PB) in older (65-85 years), women with at least one chronic illness, residing in rural communities in the Midwest. The background determinants (demographics, environmental resources, social influence, and current health) and intrapersonal determinants (motivation [intrinsic motivation and barrier self-efficacy], cognitive appraisal [illness cognition], and affective health) of physical activity will be explored in relation to physical activity behavior and cardiovascular risks as guided by a modification of the Model of Physical Activity Behavior (MPAB). Subjects will include 176 older rural volunteer women who are cognitively intact, self-described as able to perform physical activity, English speaking and who have at least one chronic illness. Recruitment will proceed through flyers, newspaper notices, and key informants in a rural, low income, Midwest County. The face to face questionnaire, administered in their homes or a location of their choosing, will include measures of background and intrapersonal determinants of physical activity. Physical activity will be measured with the Older Adult-Exercise/Physical Activity Inventory. Additionally, BMI will be determined with a weight and height scales and BP will be measured by an automated Omron 6006 monitor. Model development will proceed by systematically evaluating all the proposed relationships within the MPAB using descriptive statistics, T-tests, ANOVA, logistic correlations, stepwise regression and chi-square analysis.

REPRODUCTIVE HEALTH/DEVELOPMENTAL BIOLOGY

TITLE: Intermediate Outcomes of Hysterectomy and Alternatives AHRQ
P.I.: Miriam Kuppermann, Ph.D.
INSTITUTION: University of California San Francisco
GRANT NO.: 1R01HS11657-01A1
KEYWORDS: hysterectomy, quality of life, pelvic pain
TYPE STUDY: Outcome Research
AMOUNT: $250,000

The project expands on our existing prospective longitudinal study of 811 women with non-cancerous uterine conditions for which hysterectomy is a reasonable treatment option: abnormal bleeding, symptomatic uterine leiomyomata, and pelvic pain/endometriosis. The principal aims of the proposed study are to 1) determine whether and how intermediate-term (4-8) year clinical and quality-of-life outcomes differ by treatment group (hysterectomy, uterus-preserving surgery, or non-surgical treatments) for their uterine conditions; and 2) develop predictive models of treatment choice and satisfaction from a broad array of domains.

TITLE: Variation in Cytokine and MMP Genes and Risk of PPROM FIC
P.I.: Pedro E. Ferrand, M.D.
INSTITUTION: University of Chile
GRANT NO.: 1R01TW006197-01
KEYWORDS: preterm birth, genetics, Hispanic women
TYPE OF STUDY: Translational
AMOUNT: $17,500

Preterm Premature rupture of the membranes (PPROM) is a major cause of preterm birth and perinatal morbidity/mortality. It has been hypothesized that pro-inflammatory cytokines are important mediators of PPROM. Cytokines induce expression of matrix metalloproteinases (MMPs) that degrade the extracellular matrix, which gives the membranes their tensile strength. We hypothesize that variation in pro-inflammatory cytokine and MMP genes contributes to the risk of PROM and that gene-environment interactions amplify the risk. The long-term goal of this research is to identify genes that make significant contributions to risk of preterm premature rupture of membranes (PPROM) and how infection interacts with these genes to increase the risk of the unfavorable obstetrical outcome. The study population will be recruited from the obstetrical services of the Hospital San Borja Arriaran, Santiago, Chile (over 9,000 deliveries/year). The study will be restricted to Hispanic women, their partners and offspring. If positive results emerge from the association studies, we will examine linkage using the transmission disequilibrium test. Collectively, these studies could provide evidence for the contribution of genetic factors to the risk of preterm birth.

TITLE: Characterization of Flagellar Proteins Involved in Sperm Motility FIC
P.I.: Rossana Sapiro, M.D.
INSTITUTION: University of the Republic of Uruguay
GRANT NO.: 1R01TW006223-01
KEYWORDS: proteome, infertility, contraception
TYPE STUDY: Basic
AMOUNT: $17,500

This program will identify flagella proteins involved in sperm motility and will lend to a greater understanding of mechanisms underlying male infertility and the possible development of new contraceptors. The proteome of human sperm with motility and ultrastructural defects that mirror those of the Spag6-deficient mouse will be examined to screen for humans with SPAG6 deficiency. The knowledge gained from this research will provide a molecular framework for

understanding sperm motility defects that cause male infertility and possibly offer new avenues for contraception through the disruption of purposeful sperm motion.

TITLE: Neuroimmunology/Cytokine Alterations in Vulvodynia NICHD
P.I.: Barbara D. Reed, Ph.D.
INSTITUTION: University of Michigan at Ann Arbor, Ann Arbor, MI
GRANT NO.: 5R01HD040112-03
KEYWORDS: women's health, chronic pain, vulvodynia, clinical research
TYPE STUDY: Clinical
AMOUNT: $180,954

Hundreds of thousands of women in the United States suffer from vulvodynia a chronic burning vulvar pain of unknown cause. Millions of health care dollars are spent annually for this disorder in the United States alone, not only on management, but also on the large proportion of cases that are misdiagnosed and inadequately treated. This pain, associated with allodynia and hyperpathia, has a strong genetic predilection, with African-American women rarely being affected. The broad, long-term objectives of this proposal are to assess the differences in specific neuroimmunological characteristics between women with vulvodynia and asymptomatic controls. The specific aims include: evaluation of 1) the individual cytokine/neurokine production response to stimulation of peripheral blood; 2) local changes in nerve fiber, mast cell, Substance P and serotonin density in vulvar tissue; 3) the interactions of the systemic and local immunologic systems assessed in 1) and 2); and 4) the multivariable assessment of these laboratory factors with historical risk factors for vulvodynia to explore potential pathophysiologic mechanisms accounting for the historical risk factors identified. The research design involves a case-control evaluation of 100 women with vulvodynia, 100 controls matched for ethnicity, and 100 African-American control women, using questionnaires, physical examinations, clinical laboratory data, cytokine/neurokine levels in stimulated peripheral blood, and neuroimmunhistological assessment of vulvar, biopsy specimens for nerve fiber density, mast cells, Substance P and serotonin. Results from this study will lead to improved understanding of neuroimmunologic alterations in women with vulvodynia which will direct future therapeutic strategies for this disorder.

TITLE: Control of menstrual bleeding disturbances in women NICHD
P.I.: Ian Stewart Fraser, M.D.
INSTITUTION: Sydney Centre for Reproductive Health Research, Ashfield, AUSTRALIA
GRANT NO.: 1R01HD043192-01
KEYWORDS: Endometrial bleeding, contraception, progestogens
TYPE STUDY: Basic
AMOUNT: $100,000

This project will evaluate two promising approaches to the treatment of prolonged and frequent episodes of breakthrough bleeding which sometimes accompany the use of the implantable, progestogen-only implant Implanon. These erratic episodes of bleeding can be a major reason for discontinuation of use. There is increasing evidence that continuous exposure to progestogens results in a tendency for the endometrium to release active enzymes called matrix metalloproteinases [MMPs] which can promote premature breakdown of the tissue. Inhibition of the action of these enzymes may stabilize the endometrium and improve the bleeding pattern. A commonly used tetracycline compound, Doxycycline, has strong anti-MMP action and preliminary evidence in a mouse model of menstruation suggests that it may indeed stabilize the endometrium. There is preliminary evidence that a short course of an antiprogesterone (Mifepristone) may also stabilize the endometrium, and it is postulated that a combination of an antiprogesterone with estrogen may be even more effective. Preliminary evidence in mice indicates that estrogen exposure of the endometrium in the absence of progesterone strongly inhibits the formation of new blood vessels and simultaneous anti-progesterone exposure will mimic this situation.

TITLE: Mechanism of Vulvodynia NICHD
P.I.: Ursula Wesselmann, Ph.D.
INSTITUTION: John Hopkins University, Baltimore, MD
GRANT NO.: 1R01HD039699-02
KEYWORDS: women's health, chronic pain, neurophysiology
TYPE STUDY: Clinical
AMOUNT: $19,046

The long range objective of this research is to elucidate the pathophysiological mechanisms of vulvodynia, a chronic pain syndrome of the vaginal and vulvar area, in order to develop improved treatment strategies for alleviating chronic pain in these women, targeted at the underlying pathophysiological mechanism. We propose two approaches to gain better understanding of the pathophysiological mechanisms of vulvodynia: (1) We will develop an animal model in the rat, that will allow to study the spinal cord pathways involved in the processing of noxious input from the vagina. (2) We propose to characterize pain in patients with vulvodynia in detail. Out hypothesis is that patients with vulvodynia can be differentiated into distinct groups based on their pain characteristics, and that treatment of pain in vulvodynia will be more effective, if based on recognition of the underlying neurophysiological mechanisms.

TITLE: Development and Differentiation in Reproductive Axis NICHD
Cooperative Reproductive Sciences Research at Minority I institutions
P.I.: Director–David R. Mann, Ph.D., Morehouse School of Medicine, Atlanta, Ga
Co-director/Partner–Tony M. Plant, Ph.D., University of Pittsburgh, Specialized Cooperative Centers Programs in Reproductive Research , Pittsburgh, PA
GRANT NO.: 5U54HD41749-02
KEYWORDS: reproductive, minority institutions, developmental neurobiology, apoptosis, gene expression, biological model, cell growth regulation
TYPE STUDY: Basic science, translational, clinical
AMOUNT: $250,000

The purpose of this initiative is to form a cooperative program that will augment and strengthen the research infrastructure and research capabilities of faculty, students, and fellows at minority institutions by supporting the development of new, and/or the enhancement of ongoing, basic science, translational, and clinical research that focuses on topics deemed to be of high priority and significance because of their critical importance to reproductive health.

The Morehouse Reproductive Science Research Center consists of four research projects and an administrative core. Grant No. 1U54HD41749-01 (Development and Differentiation in Reproductive Axis), David R. Mann, is the parent grant. Grant No. 1–1U54HD41749-010001 (Hypothalamic GnRH Pulse Generator), David R. Mann. Grant No. 2--1U54HD41749-010002 (Role of Prohibitin in Follicular Development), Winston E. Thompson. Grant No. 3--1U54HD41749-010003 (Role of GnRH In Luteolysis), Rajagopala Sridaran. Grant No. 4--1U54HD41749-010004(SP Regulation of Gene Expression in Spermatogenesis), Kelwyn H. Thomas.

TITLE: Fragile X Mental Retardation Gene Premutation NICHD
P.I.: Pamela L. Mellon, Ph.D.
INSTITUTION: University of California San Diego, La Jolla, CA
GRANT NO.: 5U54HD12303-23
KEYWORDS: premature ovarian failure, genetics, women's health
TYPE STUDY: Translational
AMOUNT: $113,000

Fragile X syndrome (FRX) is one of the most frequent forms of congenital mental retardation in humans, usually resulting from lack of expression of the Fragile X Mental Retardation Gene (FMR1). Interestingly, unaffected carriers or so-called FRX premutation carriers show an increased prevalence of Premature Ovarian Failure (POF) which is generally defined as cessation of reproductive function by age 40. While it is estimated that 1% of women worldwide experience POF, the prevalence of POF in FRX premutation carriers has been reported to be 16%. On a more basic science level, the FMR1 gene is expressed in many tissues, but its function is unknown. In both male and female gonads, the gene is expressed in the germ cells. For the ovary, expression of the FMR1 gene in oogonia and oocytes could have profound implications for the regulation of oocyte number and ovarian follicular reserve which clearly can impact the cessation of reproductive function.

Three aims are proposed to: 1) characterize the cell-specific FMR1 gene expression changes in normal human and mouse ovaries through their respective reproductive cycles; 2) define the physiology of hypothalamic-pituitary-ovarian function in human female FRX premutation carriers; and 3) create a repository of genetic material and extensive phenotypic information about women with POF that could eventually be used to test other candidate genes for POF.

TITLE: Genotype/Phenotype Correlations in Infertility NICHD
P.I.: Lawrence Layman, M.D.
INSTITUTION: Medical College of Georgia
GRANT NO.: 1K24HD040287-01A1
KEYWORDS: puberty, Idiopathic Hypogonadotropic Hypogonadism, genetics, reproductive health, patient-oriented research, sex differences
TYPE STUDY: Clinical
AMOUNT: $100,000

Although infertility affects 10-15% of all individuals attempting to have children, little is known about the molecular basis of human puberty and fertility. The long-term goal of the investigator's laboratory is to elucidate the mechanisms underlying the development of normal puberty and reproductive capability by utilizing patients with infertility who possess gene mutations. Two groups of infertile patients will be studied: those with idiopathic hypogonadism (IHH) and those with normal puberty who have ovulation disorders or sperm abnormalities. Patients with IHH constitute a severe reproductive-deficient phenotype with absent puberty, low serum gonadotropins, and infertility. Most infertility patients have normal puberty, and constitute men with sperm abnormalities (azoospermia, oligospermia, and/or asthenopermia) or women with ovulation disorders. The overlying hypothesis is that identification of the genetic mutations in these groups will lead to

better understanding of: 1) which forms of IHH are hereditary; 2) whether FSH is necessary for normal sperm concentration and fertility in men, follicular development beyond the antral stage in women, and for normal androgens in both men and women; and 3) whether gene mutations affect the function of the encoded proteins. These hypotheses will be addressed by the following specific aims: 1) To test candidate genes for linkage and/or mutations in IHH patients; 2) To screen infertility patients for FSHb mutations, specifically those with abnormal semen analyses and those with ovulation disorders, likely to possess FSHb mutations; and 3) To create the mutants, express them in vitro, and determine their effects upon the encoded protein. The elucidation and analysis of gene mutations in infertile patients will be important to determine the genetic basis for some forms of infertility and to determine the underlying mechanisms of puberty and reproduction.

TITLE: Cellular and Molecular Mechanisms of Mammalian Ovulation NICHD
P.I.: Ok-Kyung Park-Sarge, Ph.D.
INSTITUTION: University of Kentucky
GRANT NO.: 1R01HD041609-01A1
KEYWORDS: ovulation, oocyte quality, progesterone receptor, meiosis, oocyte maturation
TYPE STUDY: Basic
AMOUNT: $100,000

The long-term goal of this research is to elucidate the molecular cascades of LH-induced signals within preovulatory follicles, leading to ovulation. The LH surge stimulates the synthesis of progesterone and its intracellular receptors, progesterone receptors (PRs), in the granulosa cells of preovulatory follicles. Interaction between progesterone and PRs in an autocrine/paracrine fashion is essential for ovulation. However, the exact mechanism by which ligand-dependent activation of PRs controls ovulation and thus normal reproductive cyclicity and fecundity are unknown. To gain insight into the molecular mechanisms underlying PR-mediated ovarian functions, the investigators initiated cloning of PR downstream genes in luteinizing granulosa cells. The two genes that they characterized as PR- downstream are the ligand-receptor system for pituitary adenylate cyclase activating poypeptide (PACAP): PACAP and its receptor type I (PAC_1). The temporal and spatial pattern of expression and secretion of the ligand PACAP along with the cellular localization of the receptor PAC_1 in the ovary advocates the potential significance of this ligand-receptor system for ovulatory processes. Pharmacological blockade of ligand-dependent activation of PAC_1 appears to interfere with the efficacy of LH and progesterone in bringing about ovulatory processes. Thus the working hypothesis is that PACAP-induced activation of PAC_1 mediates at least in part, PR function critical for follicular rupture with release of a meiotically mature oocyte. The immediate goal of this research is to determine the functional importance of PACAP within preovulatory follicles during the periovulatory period, using in vivo and in vitro approaches. In Aim 1, they will test whether PR-induced PACAP is critical for follicular rupture and for expression of ovulation-related genes, including proteolytic enzymes. In addition, they will identify PAC_1-downstream genes that may play an important role in follicular rupture. In Aim 2, they will determine the initial death/survival pathway(s) that is modulated by PR-induced PACAP in luteinizing granulosa cells. In Aim 3, they will test whether PR-induced PACAP regulates the polyadenylation translation capacity of meiotically maturing oocytes. The proposed studies are designed to provide functional endpoint(s) of interaction between PR-induced PACAP and PAC_1 in preovulatory follicles during the preovulatory period. Information derived from the results will allow better management of fertility, infertility, and endocrine-based disorders.

TITLE: A National Training Program in Reproductive Medicine NICHD
P.I.: Christos Coutifaris, M.D., Ph.D.
INSTITUTION: University of Pennsylvania
GRANT NO.: 1T32HD040135-01A1
KEYWORDS: obstetrics and gynecology, reproductive endocrinology, infertility, training fellowship
TYPE STUDY: Clinical
AMOUNT: $100,000

Reproductive Endocrinology and Infertility (REI) is one of the three subspecialty fellowships for advanced training after completion of a residency in Obstetrics and Gynecology. Formal certification for this advanced training in Reproductive Medicine is under the aegis of the Division of Reproductive Endocrinology and Infertility of the American Board of Obstetrics and Gynecology, Inc. (ABOG). This Board eventually awards certificates of special competence for the practice of Reproductive Endocrinology and Infertility to individuals after completion of an accredited training program and subsequent passing of a written and finally an oral examination. The Society for Reproductive Endocrinology and Infertility (SREI), the Society of Board Certified REIs, has as a major mission the support of programs involved in the selection, training and networking of fellows. It is within this framework that this research training is proposed. Research is an central feature of fellowship programs. Board approved training programs are academically rigorous and require a major commitment to research. This is the only formalized time during the training of Obstetrician/Gynecologists that such a rigorous commitment to an academic research exercise is required. More importantly, this is the only time when physicians in training have the opportunity to develop a lasting interest (and hopefully a passion) for research. This is the sole window through which the pipeline of academic reproductive medicine specialists can be kept open. Until recently, the academic development of fellows in training had been predominantly funded through clinical revenue. Unfortunately, during the past five years, financial constraints have prompted the discontinuation of many (29%) fellowship programs in REI and a reduction of total fellowship positions (by 50%) in the continuing active programs. This is occurring at a time when there is

an increase in the available academic positions and at a time of unprecedented advances in the research aspects of the field. The objective of the present proposal is to seek funding for a required two-year training period in research for three fellows per year, who are involved in meritorious research as part of their respective approved fellowship programs. It is anticipated that such support will greatly contribute to the early development of physician scientists in the field of Reproductive Medicine and will better prepare fellows to enter the pipeline of the NIH funded positions in the Reproductive Scientists Development Program and the Women's Reproductive Health Research Career Development initiative.

TITLE: Depo-Provera & BMD in Premenopausal Women NICHD
P.I.: Kathleen Clark, Ph.D.
INSTITUTION: University of Iowa
GRANT NO.: 3R01HD039100-03S1
KEYWORDS: bone mass, bone mineral density
TYPE STUDY: Clinical
AMOUNT: $183,750

Depot-medroxyprogesterone acetate. (DMPAm Depo-Provera™) is a progestin-only injectable contraception preparation that disrupts the hypothalamic-pituitary-ovarian-axis (HPO) and suppresses estradiol concentrations, possibly to levels found in postmenopausal women. This has raised concern regarding the potential adverse effect of estrogen deficiency on peak bone mineral density (BMD) in premenopausal women, increasing their risk of developing osteoporosis following menopause. The ongoing parent project is a longitudinal study evaluating changes in BMD every three months for 24 months in 275 women, 160 who receive their first DMPA injection simultaneously with study initiation, and 115 control subjects who are not using any hormonal method of contraception. The study will determine the effect of DMPA on BMD in women, aged 18 to 30, and whether DMPA-related BMD loss would be attenuated by higher calcium intakes. Further, it will describe baseline and post-injection estradiol levels, patterns of irregular bleeding and weight gain and determine whether those characteristics can identify woman at greatest risk for DMPA-related BMD loss. At baseline participants have their BMD, height, weight, and percent body fat measured, as well as blood collected for assay of estradiol concentrations. Enrollees complete a comprehensive interview detailing nutritional, lifestyle, demographic, medical, reproductive and behavioral factors that may influence BMD. Additionally, all participants are given one 90-day menstrual calendar to complete at home. At each 3-month follow-up evaluation, BMD and physical measurements are repeated and the nutrition and physical activity components of the interview updated. The menstrual calendar is collected, reviewed and a new 90-day calendar is provided. This proposal will extend the observation period of the parent study from 24 months per enrollee to a maximum of 42 months per enrollee. This longitudinal design will be continued, maintaining all methods and protocols employed in the parent study. There are few published longitudinal studies of BMD changes in women using DMPA for contraception, and none that extend beyond the 24 months. Thus, there are no studies that adequately characterize the patterns of BMD change over time. Through published cross-sectional studies, two potentially contradictory hypothesis regarding relationship between the length of DMPA use and BMD have been suggested 1) that BMD will be inversely and linearly related to length of DMPA use and 2) that BMD will decline initially but level off with continued use. These hypotheses could represent differential risks for DMPA-related bone loss and may influence clinical decisions regarding the acceptable duration of DMPA use. Extending the observational period of this study will be an efficient and cost effective means of more fully understanding DMPA-related bone changes over a period of time that, realistically, reflects the length of DMPA use by a substantial proportion of women choosing DMPA for contraception.

TITLE: Maternal Periodontitis and Adverse Pregnancy Outcome NIDCR
P.I.: Waranuch Pitiphat, M.S.
INSTITUTION: Harvard School of Dental Medicine, Boston, MA
GRANT NO.: 1R03DE14004-02
KEYWORDS: adverse pregnancy outcomes, periodontitis, women's health
TYPE STUDY: Case-Control Study
AMOUNT: $25,000

This study will evaluate whether periodontitis is a risk factor for adverse pregnancy outcomes, by adding an oral component to the ongoing Project Viva, a prospective study of 6,000 pregnant women, to evaluate this association. Maternal infection during pregnancy has been demonstrated to play an important role in etiology of preterm delivery. Periodontal infection can serve as a reservoir of gram negative anaerobic organisms and their products, and proinflammatory mediators which could target the placental membranes via systemic circulation thus leading to preterm delivery or fetal growth restriction. The primary aim of this study is to examine the effect of maternal periodontitis on length of gestation and fetal growth. The secondary aim is to explore the association between periodontitis and serum levels of TNF-alpha. The proposed prospective nested case-control study will request pre-existing radiographs from Viva participants.

VIOLENCE

TITLE: Improving Interventions for Drug Abuse-Partner Violence — NIDA
P.I.: Cynthia Connelly, Ph.D.
INSTITUTION: Children's Hospital Research Center, San Diego
GRANT NO.: 1K01DA015145-01
KEYWORDS: drug abuse prevention, health disparities, intimate partner violence, co-occurring disorders, career & development
TYPE STUDY: Clinical
AMOUNT: $100,000

Through the Mentored Career Development Award (K01) program the applicant will establish an independent program of substance abuse research focused on improving the identification and intervention for substance abuse, intimate partner violence (IPV) and co-occurring affective disorders (AD) in early intervention settings. The applicant's strong background of academic, research and nurse clinical training in substance abuse, violence, family health, and health services research provides an excellent foundation for this work. The proposed training goals provide additional instruction and mentoring in 1) the complex linkage between ATOD, IPV, and AD and engagement and treatment strategies for early preventative intervention, 2) longitudinal data analysis and modeling techniques, 3) cultural issues and health disparities that complicate early intervention efforts among diverse populations, and 4) training in the ethical conduct of research. This training will prepare the applicant to pursue a research career in prevention science targeting substance abuse among women of childbearing age. In Phase I secondary data analysis will be conducted on longitudinal data provided by two large samples of postpartum women to examine the role of ATOD, IPV, and AD on engagement and participation with an early intervention: home visitation. Subgroup analyses based on age, race/ethnicity and combinations of ATOD, IPV, and AD will be examined. In Phase II, existing protocols for provider education and training in assessment including instrumentation, interpretation, and triage will be critically examined in two model programs. Phase III will use findings from Phases I and II as well as mentoring from experts in specific content areas to inform the development of strategies and preliminary protocols to strengthen early preventative interventions addressing these specific issues and to pilot test these protocols. Phase III will identify characteristics that impact implementation at the provider, family and program level and will generate preliminary data to inform research and program development. The data will form the basis for a R01 application to prospectively test the effectiveness of strategies designed to improve provider education and practice related to ATOD, IPV, and AD among women of childbearing age.